The New England
Journal of Medicine

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Volume 243 NOVEMBER 30, 1950 Number 22

THE ELECTROCARDIOGRAM AND DISTURBANCE OF POTASSIUM METABOLISM*

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BOSTON

A SIZABLE literature demonstrating electrocardiographic abnormalities in various disorders of potassium metabolism has developed in the last ten years. The earlier observations suggested a correlation between serum potassium levels and electrocardiographic changes.[1-12] As we have observed more cases, however, it has become apparent that electrocardiographic findings and serum potassium concentrations do not always correlate.[13] Since potassium is primarily an intracellular ion and presumably exerts its major physiologic effects within cells, a lack of correlation might be anticipated.

The question then arises whether intracellular fluid potassium concentrations correlate better than concentrations in serum with the alterations of the electrocardiogram in patients whose potassium balance is disturbed. No clinical data are yet available to relate such changes with directly measured intracellular potassium concentration. The cases presented below emphasize the lack of correlation that may be present between extracellular potassium concentration and electrocardiographic changes. On the basis of indirect evidence an attempt is made to relate presumed changes in intracellular content with alterations in the electrocardiographic patterns.

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CASE REPORTS

CASE 1§ (*Chronic Nephritis and Periodic Muscular Paralysis*). J. F., a 40-year-old laborer, was first seen at the Massachusetts General Hospital in October, 1943, on the Neurological Service because of severe muscular weakness of 3 days' duration. Physical examination was not remarkable except for profound weakness, and a diagnosis of radiculomyelitis was made. The weakness disappeared after 2 days, and he was discharged.

TABLE 1. *Pertinent Chemical Determinations in Case 1.*

DATE	SERUM CHLORIDE *milliequiv./liter*	SERUM CARBON DIOXIDE *milliequiv./liter*	SERUM SODIUM *milliequiv./liter*	SERUM CALCIUM *mg./100 cc.*	SERUM PHOSPHORUS *mg./100 cc.*	SERUM POTASSIUM *milliequiv./liter*	ERYTHROCYTE POTASSIUM *milliequiv./liter*
11/12/43*	108	—	—	9.2	—	—	—
11/27/43	—	—	—	10.5	3.0	2.5	—
12/ 2/43	110	—	—	—	—	2.9	—
10/ 3/44	110	22	143	9.0	1.8	4.5	—
12/29/44†	110	19	142	—	—	5.2	—
1/13/45	100	32	—	—	3.5	—	—
3/30/48	109	23	—	9.2	2.5	4.0	—
5/ 5/49†	106	14	129	8.8	1.9	1.8	—
5/ 6/49*	—	—	—	—	—	1.3	85.0
10/ 4/49	—	—	146	—	—	3.0	84.5

*Muscle paresis (++).
†Muscle paresis (+++).

One month later he was re-admitted to the hospital because of recurrent paresis. He had passed a kidney stone in the interim. The blood pressure was 120/70. The physical findings were again quite normal except for generalized muscular paresis. Urinalysis revealed a ++ test for albumin, and the sediment contained both erythrocytes and leukocytes in moderate numbers. The phenolsulfonphthalein excretion was 40 per cent in the first 15 minutes and 80 per cent in 2 hours. On x-ray study several small areas of calcification were considered to be present in the kidney parenchyma. Culture of urine from the left kidney revealed a moderate growth of *Escherichia coli*. The serum potassium was 2.5 milliequiv. per liter (Table 1). An electrocardiogram demonstrated low to isoelectric T waves. A diagnosis of chronic pyelonephritis with a "low-potassium syndrome" was made. The patient was discharged on sodium citrate, potassium citrate and calcium gluconate.

In December, 1944, he was readmitted to the hospital because of muscular weakness. He had taken no alkalizing salts for several months. It is of interest that the serum potassium (Table 1) was normal, and the electrocardiogram (Fig. 1) abnormal at the time of muscular paresis on this

§Reported briefly in a previous publication.[8]

entry. He was again placed on the alkalizing salts by mouth, and 2 weeks later the electrocardiogram was normal (Fig. 1).

He did well until May, 1949, when the paralysis recurred 1 month after a reduction in the dosage of sodium citrate. At this time a reduction in serum potassium and abnormalities of the electrocardiogram were both found in association with muscle weakness. He was placed on 2 gm. each of potassium and sodium citrate three times a day and again showed rapid improvement. He was last seen in October, 1949, feeling quite fit. The electrocardiogram was within normal limits at this time, although the serum potassium concentration was slightly low.

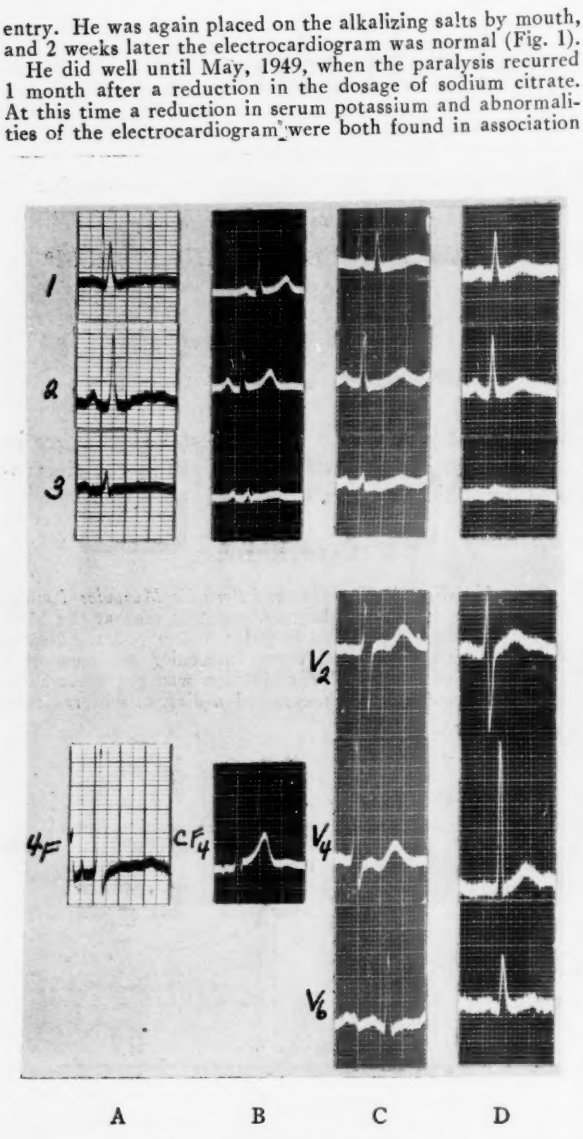

FIGURE 1. *Electrocardiograms in Case 1.*

A — *tracing taken at the time of muscle paralysis demonstrating low to isoelectric T waves and suggestive U waves in Leads 2 and 4F (the serum potassium was 5.2 milliequiv. per liter).*

B — *tracing two weeks later while sodium and potassium citrate were being taken by mouth and with normal muscular strength.*

C — *tracing made at the time of moderate muscle paresis two hours after a dose of 15 cc. of a solution containing 50 per cent potassium citrate (the serum potassium was 1.8 milliequiv. per liter). The prolonged QT interval of 0.50 second and depression of the RS–T segments in Leads 2, 3 and V4 should be noted).*

D — *tracing made after good clinical improvement but while the patient was receiving no potassium citrate by mouth. This is quite normal although the T waves are lower than those in* B *(the serum potassium was slightly low—3.0 milliequiv. per liter).*

The diagnosis in this case seems quite definitely to have been chronic pyelonephritis and a periodic low potassium syndrome. The loss of fixed base through the kidney resulted in clinical evidence of potassium deficiency. It is of interest that the electrocardiogram correlated with the muscular strength more accurately than the level of serum potassium, which, on two occasions, was at variance with what one might have expected from the clinical condition.

CASE 2 (*Sprue*). A 27-year-old housewife entered the hospital on December 5, 1948, complaining of diarrhea of 6 months' duration. One month before entry soreness of the tongue, dryness of the mouth and inflammation of the conjunctivas developed. She had noted profound weakness and a weight loss totaling 30 pounds.

Physical examination revealed a very thin, cachectic woman with redness of both conjunctivas and redness and swelling of all the mucous membranes, including the tongue. The papillae of the tongue were atrophic. The blood pressure was difficult to obtain; the systolic pressure was measured at 75 by palpation but was not obtainable by auscultation. The pulse was regular at 110. The weight was 73 pounds. The abdomen was scaphoid and nontender, and the peristaltic waves were visible by inspection. Significant atrophy of the extremities was present, and the muscular force was very feeble.

Examination of the blood demonstrated a hemoglobin of 14 gm. and a white-cell count of 11,000. The hematocrit was 42 per cent. The urine was not remarkable. Blood chemical studies were as follows: total protein 4.3 gm., albumin 2.5 gm., globulin 1.8 gm., and nonprotein nitrogen 21 mg. per 100 cc., sodium 126 milliequiv., and chloride 95 milliequiv. per liter, cholesterol 126 mg., calcium 7.0 mg., phosphorus 1.8 mg., and alkaline phosphatase 5.4 Bodansky units per 100 cc. The basal metabolic rate was +5 per cent. Duodenal drainage revealed the duodenal juices to be deficient in pancreatic enzymes. The stool loss averaged about 60 gm. of fat per day. The potassium on the day that the electrocardiogram was taken was 4.3 milliequiv. per liter (Fig. 2).

The patient was placed on a nutritious diet with supplements from skimmed milk, crude liver extract intramuscularly and brewer's yeast. After 1 month's treatment she had gained 15 pounds in weight. An electrocardiogram taken at the time of maximal clinical improvement, as contrasted with the tracing obtained soon after admission, is demonstrated in Figure 2.

The interesting feature of this case is the finding of an abnormal electrocardiogram on entry, consistent with potassium deficiency despite the normal serum potassium concentration. Balance studies on patients such as this have shown significant losses of potassium in stools and urine[10-12, 14, 15] during periods of illness, and presumably this patient had sustained similar losses. Thus, the first electrocardiogram may have reflected an intracellular potassium deficit, being uninfluenced by the normal extracellular potassium concentration. After adequate nourishment and weight gain, both the electrocardiogram and the serum potassium concentration were normal.

CASE 3 (*Pan-hypopituitarism with Adrenal Insufficiency*). E. B., a 42-year-old housewife entered the hospital on May 2, 1949, complaining of weakness and weight loss. Eight years before entry she had had a uterine hemorrhage shortly after the delivery of her first and only child. Within 4 months loss of weight, weakness and loss of hair developed, and menstruation failed to return. Since then the patient had had recurrent hospital admissions, which had included

four episodes of coma, one of which was associated with a blood sugar of 36 mg. per 100 cc.

Physical examination revealed a thin, frail woman, whose blood pressure was 105/65. The skin was soft and delicate. Axillary hair was absent, and only scant pubic hair was noted. The heart and lungs were normal. The breasts were atrophic. The body weight was 80 pounds.

Laboratory studies indicated a hemoglobin of 12.5 gm. Examination of the urine was normal. The basal metabolic rate was −28 per cent. The serum concentrations of sodium, potassium, calcium and protein were below normal (Table 2).

The patient was placed on a high-carbohydrate, low-potassium diet containing about 8 gm. of sodium chloride with six feedings a day. Lipoadrenal cortical extract was given, and on May 18, 30 mg. of thyroid and 10 mg. of methyltestosterone were added daily.

On May 23 considerable nausea, vomiting and drowsiness developed, and the blood pressure was found to be low. An intravenous infusion of saline solution, glucose and aqueous adrenocortical extract was given. The blood chemical analyses of May 25 are seen in Table 2. Two days later it was decided that the incorporation of potassium in the intravenous infusion of fluid might be of value, and 1 liter of water containing 55 milliequiv. of potassium, 38 milliequiv. of sodium, with chloride as the chief anion, and 10 per cent dextrose was given over a 12-hour period. Eight hours after the beginning of the infusion the clinical condition was improved in spite of the remarkable alteration of the blood chemical values (Table 2). An electrocardiogram taken at this time is illustrated in Figure 3. The blood pressure was 60/0 on May 25, 120/70 on May 27, 85/60 on May 28 and 100/70 on May 31. Improvement continued, and on June 1, two 75-mg. pellets of DCA (desoxycorticosterone acetate) were implanted. The patient was discharged on June 6, receiving 10 mg. of methyltestosterone and 60 mg. of thyroid per day.

Panhypopituitarism had resulted in deficiency of adrenal and thyroid activity, each of which might have affected the electrocardiogram. The low T waves could in part, at least, have been associated with hypothyroidism, although there was no evidence that myxedema was present. The potassium solution was administered at a time when the patient was critically ill because it was thought that an intracellular potassium deficit had resulted from the low-potassium diet and the rather vigorous treatment with sodium chloride and DCA. The clinical condition was improved, and the electrocardiogram apparently not appreciably affected by the remarkably high serum potassium and low serum sodium concentrations found during the infusion of potassium.

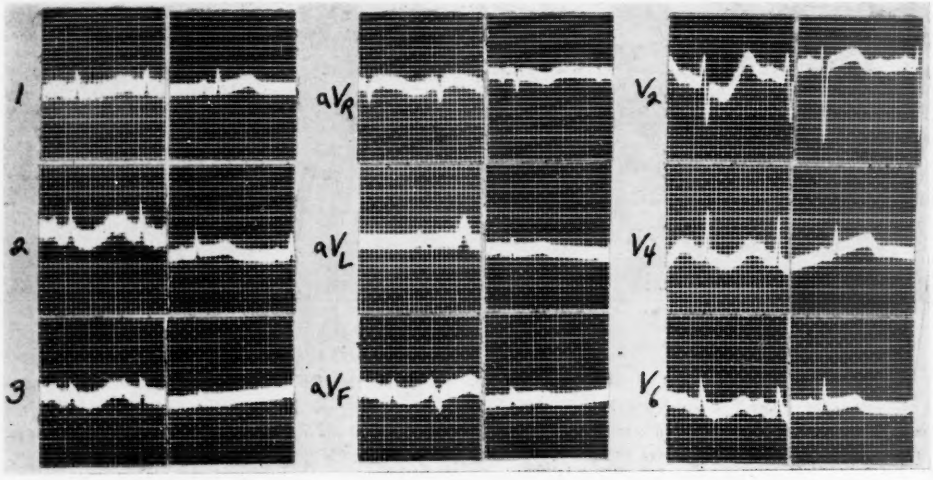

FIGURE 2. *Electrocardiograms in Case 2.*

A — *tracings taken on December 8, 1948, revealing depression of the RS–T segments, particularly in Leads* V_2 *and* V_4. *Extrasystoles are apparent in* aV_L *and* aV_F. *The prolonged QT interval may have resulted from both calcium and potassium deficiency even though the serum potassium was normal (4.3 milliequiv. per liter).*

B — *normal tracing at the time of maximal clinical improvement (February 2, 1949).*

CASE 4 (*Ureterocolostomy and Vomiting*). E. S., a 64-year-old man, was admitted to the hospital on May 9, 1949, because of abdominal pain and vomiting. One month before entry he had had a complete resection of the bladder, with transplantation of the ureters into the large bowel.

Physical examination revealed a chronically ill man. The skin was dry, but the mucous membranes appeared well hydrated. The heart was normal; the blood pressure was 130/85. Moderate tenderness was elicited in the right lower quadrant of the abdomen.

Laboratory studies showed a hemoglobin of 10 gm. An intravenous pyelogram demonstrated prompt filling of the renal pelves with dye, and no evidence of obstruction was noted. Gallstones were demonstrated by an x-ray film. Blood chemical studies on admission and through the hospital course are presented in Table 3.

The patient continued to vomit periodically, and for this reason saline solution and glucose were given parenterally. A rising blood nonprotein nitrogen during the next week was taken as an indication of urinary-tract obstruction. A right ureterostomy was done on June 7. On June 8 icterus was noted. During an exploratory laparotomy a catheter was placed in the common duct.

The patient continued to feel poorly and required 3 or 4 liters of parenterally administered fluid daily to maintain

hydration. Two 500-cc. blood transfusions were given. On June 20 the blood pressure fell to below normal, and the heart sounds were faint. The serum potassium concentration ranged between 0.9 and 1.3 milliequiv. per liter, and yet on June 21 the electrocardiogram (Fig. 4) showed wide T waves of quite good amplitude, although the RS-T segments were depressed and electrical systole was prolonged. On June 24 definite tetany was noted. Moist rales were audible at the lung bases, and edema of the extremities was present. In spite of supportive treatment the patient died the next day.

FIGURE 3. *Electrocardiograms in Case 3.*

A — *apparently normal tracing taken on May 27, 1949, during an intravenous infusion of a solution containing potassium and sodium. The serum potassium was 12.7, and the sodium 104 milliequiv. per liter during this infusion. A tracing the day before was not unlike this one.*

B — *tracing taken one week later after vigorous and adequate treatment for hypoadrenalism, revealing lower T waves at a time when the serum potassium was normal (4.1 milliequiv. per liter).*

A serious disturbance of extracellular electrolyte concentration was evident in the course of this complicated illness. Of particular note was the drop in serum potassium concentration. Despite this profound lowering of extracellular potassium the electrocardiogram revealed T waves of good amplitude but of increased duration. Furthermore, the development of tetany indicated that muscle irritability was increased. The ratio of potassium to calcium in respect to muscle contractility may have been important, as originally observed by Ringer.[17] The low serum potassium concentration coincident with appreciable nitrogen retention is of interest.

CASE 5 (*Adrenocortical Virilism and Addison's Disease*). A 12-day-old infant was referred from another hospital because of pseudohermaphroditism and suspected Addison's disease. One and a half years before the patient's birth a sibling had been born with an enlarged clitoris. This sibling had died at the age of 2 days, and post-mortem examination had shown hypertrophy of the adrenal cortexes. The present patient weighed 3.4 kg. at birth and appeared vigorous but showed clitoral or penile hypertrophy, a urogenital sinus and paramedian structures resembling a bifid scrotum.

TABLE 2. *Pertinent Chemical Determinations in Case 3.*

DATE	TOTAL PROTEIN	NONPROTEIN NITROGEN	SERUM SODIUM	SERUM CHLORIDE	SERUM CARBON DIOXIDE	SERUM POTASSIUM
	gm./100 cc.	*mg./100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
May 3	6.0	19	132	98	29	3.8
May 6	6.3	—	130	94	—	4.8
May 9	—	—	137	102	—	3.8
May 19	—	—	135	100	—	—
May 25	—	—	112	76	—	4.3
May 27	—	—	{103* 105	83*	—	12.7*
May 28	—	—	128	83	—	4.5
May 31	—	—	143	92	—	4.2
June 3	—	21	144	103	37	4.1

*During infusion of glucose, potassium and sodium.

In addition, there was brownish pigmentation of the skin, particularly noticeable in the areolae and perineum.

The child did well until the 4th day of life, when vomiting and diarrhea occurred, accompanied by rapid weight loss. Suspecting adrenocortical insufficiency, the attending physician gave daily clyses of normal saline solution and 1 mg. of DCA intramuscularly and added 3 gm. of sodium chloride to the daily formula. Some improvement was noted after these measures, but listlessness and poor weight gain occasioned admission to this hospital on the 12th day of life.

On entry the infant's condition was poor. The weight was 2.92 kg., and the temperature was normal. Respirations and pulse were irregular. There was evidence of moderate dehydration. Anomalies of the external genitalia, as previously described, were noted.

Laboratory studies were limited by the critical condition of the infant, as well as by the fact that admission occurred on a holiday afternoon. The chief differential diagnosis in terms of immediate therapy lay between potassium intoxication as a result of a lack of adrenal "sodium-potassium" hormone and potassium deficiency developing from overvigorous DCA and sodium chloride treatment. The electrocardiogram gave immediate and striking information on this point. It showed a slow, idioventricular rhythm, with widening of the intraventricular conduction, high T waves and absent P waves consistent with potassium intoxication (Fig. 5). The infant was immediately treated intravenously with a solution containing sodium chloride and dextrose, to which aqueous adrenocortical extract was added in sufficient amounts to give a dose of 100 cc. per square meter per 24 hours.

The clinical response was dramatic. Within 1 hour's time the pulse was regular and full, the color was good, and the child had become more active. Serial electrocardiograms taken at frequent intervals gave evidence of restoration of electrolyte equilibrium.

Potassium intoxication was quite evident from the initial electrocardiogram and indicated that previous treatment had been inadequate to overcome the deficiency of adrenal "sodium-potassium" hormone. Response to treatment was gratifying both clinically and by electrocardiogram. Unfortunately, measurements of the serum potassium concentration are not available for correlation with the electrocardiograms, although presumably both intracellular and extracellular potassium concentrations may have been elevated at the time of the first electrocardiogram.

Case 6 (*Addison's Disease and Idiopathic Hypoparathyroidism*). An 8-year-old girl was admitted to the Massachusetts General Hospital in March, 1942, with a diagnosis of Addison's disease. Her symptoms had been fatigue and weight loss for 8 months.

Physical examination revealed pigmentation of the face, knees, elbows and hands typical of Addison's disease. The remainder of the physical examination was not remarkable. The blood pressure was 106/70.

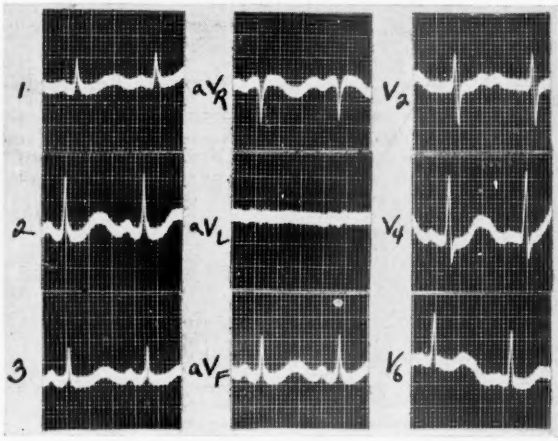

FIGURE 4. *Electrocardiogram in Case 4, Demonstrating Wide T Waves, Depression of Some RS–T Segments and a Prolonged QT interval of 0.48 Second.*

The serum potassium and calcium were both unusually low — 1.3 milliequiv. per liter and 3.6 mg. per 100 cc., respectively. Deficiency of either calcium or potassium could account for the prolonged QT interval, although the wide T waves, together with depression of the RS–T segments in some leads, are perhaps more suggestive of potassium deficiency.[16]

She was observed on the metabolic ward, where comprehensive studies were carried out.[18] Her condition during the study period was good, and she experienced no unusual weakness or fatigue. She was treated with 50 mg. of testosterone propionate daily. After 17 days of this treatment an electrocardiogram was taken (Fig. 6). Simultaneous blood studies revealed a calcium of 7.1 mg., inorganic phosphorus of 8.5 mg. and nonprotein nitrogen of 15 mg. per 100 cc. and a serum potassium concentration of 0.7 milliequiv. per liter. While the electrocardiogram showed prolongation of the QT interval (0.38 second), probably as a result of the calcium deficiency, the T waves appeared quite normal. After the omission of testosterone for 3 days, the serum potassium was 4.7 milliequiv. per liter.

TABLE 2 (*Concluded*).

Date	Fasting Blood Sugar	Serum Cholesterol	Serum Calcium	Serum Phosphorus	Serum Alkaline Phosphatase
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*Bodansky units*
May 3	53	217	7.5	2.6	3.6
May 6	—	—	—	—	—
May 9	74	—	—	—	—
May 19	88	—	—	—	—
May 25	92	—	—	—	—
May 27	170*	—	—	—	—
May 28	—	—	—	—	—
May 31	72	—	—	—	—
June 3	70	—	—	—	—

This case illustrates again the unreliability of the serum potassium level as an index of over-all potassium metabolism. The facts that the clinical condition of the patient and the electrocardiogram were normal suggest that the amount of potassium in the cells was at least adequate. Testosterone is well known[18] to encourage the transfer of serum potassium into the body cells, where it promotes protoplasmic anabolism. The only electrocardiographic abnormality at the time of maximal lowering of serum potassium concentration was the prolonged electrical systole. This was probably related to the calcium deficiency attendant upon hypoparathyroidism.

TABLE 3. *Pertinent Chemical Determinations in Case 4.*

DATE	NONPROTEIN NITROGEN *mg./100 cc.*	SERUM CHLORIDE *milliequiv./liter*	SERUM CARBON DIOXIDE *milliequiv./liter*	TOTAL PROTEIN *gm./100 cc.*	SERUM ALBUMIN *gm./100 cc.*
May 10*	58	104	23	5.8	—
May 11†	30	102	20	—	—
May 17	26	—	—	4.8	2.7
May 19	—	—	—	—	—
May 22	44	106	—	5.0	—
May 30‡	35	103	24	5.6	2.8
June 6	90	114	18	4.9	—
June 17	112	96	14	—	—
June 18	110	95	16	—	—
June 21	120	69	19	4.4	—
June 22	130	78	21	—	—
June 23	—	98	18	—	—

*Hemoglobin 10 gm. per 100 cc. on this day.
†Hemoglobin 9.8 gm. per 100 cc. on this day.
‡Hemoglobin 11.2 gm. per 100 cc. on this day.

DISCUSSION

The cases presented constitute an assortment of pathologic states that have in common disturbance of electrolyte balance, particularly of potassium. These alterations are at times associated with significant and characteristic changes in the patient's clinical condition (Case 1). More often the clinical manifestations of the disturbance are not diagnostic (Cases 2, 4 and 5); sometimes, there may be few or no clinical manifestations of profound alterations of potassium metabolism (Cases 3 and 6).

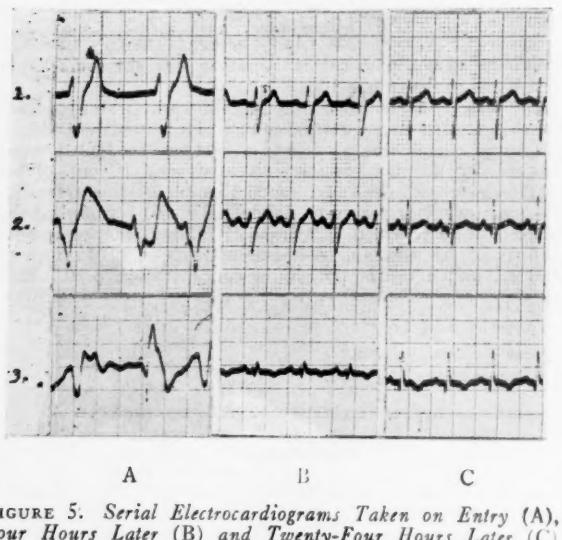

FIGURE 5. *Serial Electrocardiograms Taken on Entry* (A), *Four Hours Later* (B) *and Twenty-Four Hours Later* (C) *in Case 5, Demonstrating a Marked Widening of the QRS Complexes, High T Waves and Absent P Waves, with an Idioventricular Rhythm Indicating Potassium Intoxication.*

In four hours the change is dramatic, with a relatively normal tracing although the QRS interval decreased further after twenty-four hours.

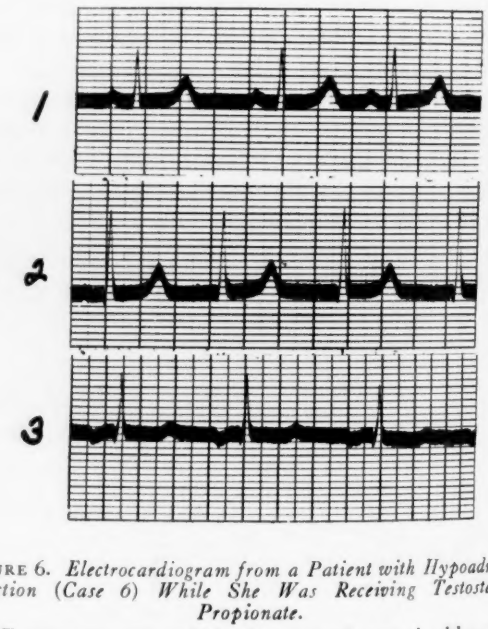

FIGURE 6. *Electrocardiogram from a Patient with Hypoadrenal Function (Case 6) While She Was Receiving Testosterone Propionate.*

The T waves are quite within the range of normal, although in Leads 1 and 2 they are rather "peaked." The prolonged QT interval of 0.38 second (normal, 0.35 second) was considered to be a result of calcium deficiency secondary to hypoparathyroidism. The serum potassium was unusually low — 0.7 milliequiv. per liter.

Certain laboratory tests give aid in defining the status of an individual patient, so that rational treatment may be prescribed. Unfortunately, there are some limitations in the presently available clinically applicable technics. Potassium, for instance, is primarily an intracellular ion with a concentration about thirty times as great in cellular fluid as in interstitial fluid. Direct measurements of intracellular potassium are not yet available for routine clinical use. The concentration of potassium in extracellular fluid or plasma reflects merely the equilibrium pertaining at any given time between gastrointestinal absorption, cell metabolism with movement either into or out of intracellular fluid and urinary excretion of the ion. Thus, at one time a high concentration of serum potassium may reflect assimilation in excess of renal excretion, even though cell stores are low or normal (Case 3). At other times, movement of potassium from cells may result in normal extracellular concentrations correlated with progressive intracellular depletion of potassium (Cases 1 and 2). Chemical estimation of serum potassium concentration may thus give little information concerning the potassium concentration in cells.

Darrow[19, 20] and others[21-23] have called attention to the correlation between extracellular hypochloremic alkalosis and intracellular depletion of potassium. When one finds an elevation of serum bicarbonate and pH in association with a low serum chloride concentration, intracellular potassium may be assumed to be low. However, intracellular potassium depletion may exist independently of this alteration (Cases 1 and 2).

In not all conditions is the loss of potassium from the body necessary for significant symptoms to appear. During or preceding an exacerbation of familial periodic paralysis no loss of potassium from the body has been detected.[24] It seems, therefore, that during a period of paralysis either potassium "lost" to some compartment of the body, possibly the liver, or the demand for potassium in the muscle cells is such that the extracellular fluid cannot supply an adequate amount. On the basis of the data of Case 6 it seems unlikely that in periodic paralysis the loss of extracellular potassium alone could result in muscular paralysis. The abnormal electrocardiogram during an attack of paralysis suggests a deficiency of muscular potassium.

TABLE 3 (*Concluded*).

DATE	SERUM GLOBULIN *gm./100 cc.*	SERUM SODIUM *milliequiv./liter*	SERUM POTASSIUM *milliequiv./liter*	SERUM CALCIUM *mg./100 cc.*	SERUM PHOSPHORUS *mg./100 cc.*
May 10*	—	—	—	—	—
May 11†	—	134	3.9	—	2.2
May 17	2.1	132	—	6.8	—
May 19	—	—	2.8	—	—
May 22	—	137	—	—	—
May 30‡	2.8	—	—	—	—
June 6	—	150	—	—	—
June 17	—	—	—	—	—
June 18	—	130	—	—	—
June 21	—	116	1.3	3.8	7.6
June 22	—	—	—	—	—
June 23	—	136	1.2	—	—

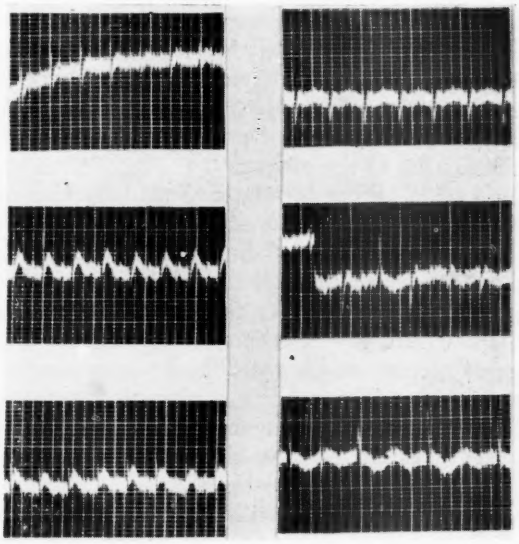

FIGURE 7. *Electrocardiograms of a Young Rat, Illustrating the Changes Induced by a Potassium-Deficient Diet.*[26]

A *shows the tracings on a normal diet, and* B *those on the same diet except for potassium deficiency. Note the prolongation of the PR and QRS intervals as compared with the normal tracing. The QRS complexes vary considerably in shape. The T waves are isoelectric or inverted.*

Direct correlation of electrocardiographic changes with tissue analyses is difficult and can best be done on animals. Gardner[25] has carried out careful tissue analyses on rats maintained on a potassium-

deficient diet and observed a significant decrease (28 per cent) in skeletal-muscle potassium and an increase in sodium content. Studies carried out on a similar diet[26] with young rats revealed significant electrocardiographic changes in one week and are illustrated in Figure 7. Significant impairment of auriculoventricular and intraventricular conduction were noted, usually with slowing of the heart rate. The T waves become isoelectric or inverted. It should be noted, however, that skeletal muscle and cardiac muscle are not always comparable in glycogen or electrolyte content.

It is also known that sodium from extracellular sources may take up the intracellular position of potassium in states of depletion of the latter ion.[27, 28] The concentration of extracellular sodium is dependent upon so many other factors, however, that a lowering of serum sodium concentration cannot be relied upon as an index of intracellular potassium deficit.

The increasing use of potassium-containing fluids in the treatment of patients with derangements of the electrolyte pattern is creating an urgent need for methods of measuring potassium in cells. The inadequacy of methods of estimating cell potassium by means of characteristic alterations of the extracellular electrolyte pattern is emphasized by the cases presented above. The electrocardiogram appears to give a rapid and reasonably reliable index of presumed qualitative changes in intracellular potassium concentration. In this regard the electrocardiogram is helpful not only in prescribing the appropriate type of therapy in many cases but also in detecting early signs of potassium excess in the administration of therapy.

The lack of direct correlation found by Crismon et al.[29] between cardiac-muscle potassium content and electrocardiographic abnormalities during potassium poisoning produced by infusion is of interest. It is possible that the critical level where potassium intoxication occurs is close to the upper range of normal, making it difficult to demonstrate a correlation. The studies during potassium deficiency[25, 26] are more suggestive of a correlation between electrocardiographic abnormalities and intracellular potassium content.

The electrocardiogram is of limited value when alteration of the normal pattern has resulted from structural heart disease — for example, impairment of intraventricular conduction in coronary-artery disease.

Summary

A variety of diseases are presented in which alterations of electrolyte balance, including potassium metabolism, are apparent. Lack of correlation between electrocardiographic abnormalities and serum potassium levels is manifest. Indirect evidence is presented from the analysis of clinical cases that intracellular potassium content may be correlated with both the clinical condition of the patient and the electrocardiographic changes. The value of the electrocardiogram as an aid in handling certain patients with disturbed potassium metabolism is illustrated.

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EPISACROILIAC LIPOMA AS A CAUSE OF LOW-BACK PAIN*

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LOW-back pain has long been one of the common symptoms confronting practicing physicians. Its causes are numerous, extending into almost every specialized sphere of medical and surgical interest. Inasmuch as many disorders manifest themselves as the clinical symptom of low-back pain, progress in this field is made with the recognition of distinct etiologic entities lending themselves to sure diagnosis and specific treatment. In recent years the presence of painful, tender lobules of fat as one cause of low-back pain has been recognized with increasing frequency. From recent reports in the literature and from our own experience, it appears probable that this entity deserves prominence as a major cause of the elusive clinical symptom of low-back pain. We are reporting several cases recently encountered, with 1 illustrative case report, that highlight some of the features of these fatty tumors.

CASE REPORT

CASE 1. A 53-year-old housewife was examined on November 23, 1946, because of the complaint of dull pain over the right lower portion of the back, of relatively sudden onset and persisting for the previous 2 weeks. She recalled that 2 years previously she had experienced similar pain on the left side, lasting 1 week and clearing spontaneously. The past history was noncontributory except for a subtotal thyroidectomy 15 years previously. The patient was obese, weighing 189 pounds. Examination of the body generally was negative. Over the right sacroiliac articulation, a moderately deeply placed, tender, firm mass, measuring 4 by 2 cm., could be palpated. Local infiltration of the subcutaneous nodule with 2 per cent procaine solution did not diminish the pain. Admitted to the Boston City Hospital, the patient was operated upon under local anesthesia. A discrete mass was found herniated through deep fascia, with a pedicle present. The pedicle was cut, the mass removed, and the rent in the fascia repaired. The pain promptly disappeared after this procedure. Examination of the specimen showed it to consist of normal-appearing fatty tissue.

This patient was seen again on May 13, 1949, when she stated that for the previous week she had been experiencing pain over the left lower portion of the back identical to that which had previously been felt on the right side. The pain was noted to be worse while she was upright and was relieved when she was lying down. Examination revealed a tender, subcutaneous mass overlying the left sacroiliac joint in a position similar to that of the scar of the previous operation. This mass was not as well defined as the other had been. Readmitted to the Boston City Hospital, the patient was again operated upon. No definite fatty tumor or herniation was made out at this time. A fairly wide excision of fibrofatty tissue in the involved area was done, complete relief of symptoms occurring thereafter. On re-examination, 6 months later, the patient reported persistent relief from pain.

DISCUSSION

In 1935 Sutro[1] reported on the high incidence of subcutaneous nodes in the sacroiliac region. They were present in 94 of his series of 170 unselected hospital patients, and of this number, 33 had low-back pain. On operation on 4 of these patients, lobules of apparently normal fat were discovered and removed. In 1 case there was complete cessation of low-back pain. Sutro assumed that these pads, although tender, were protective buffers. Apparently, their full significance as possible causes of low-back pain was not appreciated.

Two years later Ries[2] gave more significance to the tender nodules of fat. He reported a series of 1000 unselected patients, a third of whom had lumbosacral backache. Approximately half those with backache were found to have subcutaneous lumbosacral tumors. An equal number had asymptomatic tumors in the same location. On surgical removal the painful tumors proved to be lipomas with a fibrous capsule. Ries designated these as episacroiliac lipomas.

These entities, or similar painful nodules, came subsequently to be designated as "fibrositis," particularly in the British literature. On removing such nodules from the backs of 10 men in the British armed forces, Copeman and Ackerman[3] found all to be fatty tumors. In each case removal caused a striking relief of symptoms. These investigators then performed an anatomic study on the backs of 14 cadavers and noted that in all — even in the most cachectic — a basic fat pattern was present. Roughly, this constant fat pattern lay above and medial to the scapulas. It then ran along the lateral aspect of the lumbar and sacral erector-spinae musculature and thence out from the sacroiliac joints along the posterior wings of the iliums. In a study of 50 trigger points in so-called cases of fibrositis, there was a close correlation with the lumbar, sacral and iliac portions of this basic fat pattern.

In a later paper Copeman and Ackerman[4] noted that in the distribution of the basic fat pattern, localized areas of fibro-fatty tissue may, for some reason, become edematous. Because of the unyielding nature of the fibrous investment, painful tension may then be set up. If such tensions continue herniation through the overlying fascia, particularly in areas of potential fascial weakness, may result.

Herz[5, 6] also did anatomic studies of the backs of cadavers and agreed with the basic fat-pattern concept of Copeman and Ackerman. He found that in obese persons the fat pattern tended to be obscured by a more generalized deposition of fat. He observed that the fascias were not of uniform thickness, being notably thinner in some places than in others, frequent actual deficiency of fascial membranes being present. In these places, the underly-

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ing fat tended to bulge through, occasionally resulting in complete herniation. This might not give rise to symptoms until some incident such as sudden trauma or some illness that required lying on the back for several days produced an increase in the fat pressure and a painful degree of distention. This, in turn, might lead to edema and perpetuation of the condition.

He noted that the apparent tendency to thinning of the fascia when a greater quantity of fat is present is a possible explanation of the fact that clinically the incidence of low-back pain from this cause is much greater in obese women than in any other group. At operation, in many cases, it was not possible to demonstrate a definite mass to correspond with the palpable nodule; a wide dissection of fat was carried out nevertheless. Pathologically, the specimens varied from normal adipose tissue — with or without a pedicle — to edematous, hyperemic fat, which showed inflammatory changes in microscopical sections.[4, 5]

Our own experience, as indicated by the foregoing case report and Table 1, closely parallels that of others who have reported on this entity. Although they have been described as occurring in other areas of the back, it appears that the lower back and the sacroiliac areas in particular are the most frequent sites for these painful lobules of fat to appear (Table 1). Obesity has been so frequently encountered among patients with this condition that it is necessary to ascribe to it an etiologic role. The ease with which the painful nodules may be felt by the examiner, especially with his attention directed to the appropriate area by the patient as the central site of pain, makes it possible for the condition to be promptly diagnosed, and appropriate treatment instituted. Our patients usually sought medical attention after experiencing pain for only a few weeks. An outstanding exception was Case 3. This patient had weighed 110 pounds at the time of her marriage twenty-two years previously. Soon thereafter she gained considerable weight in a short time, weighing 235 pounds at the time of examination. She stated that her low-back pain had been present ever since the initial period of weight gain. Despite the lengthy duration of pain, surgical excision of the mass resulted in as prompt relief of symptoms as that in patients with pains of more recent onset. Although local infiltration with procaine hydrochloride and physiotherapeutic measures, such as heat and massage, have been described as helpful in 50 per cent of these cases,[7] these principles have been disappointing when applied to our patients. We have found local excision to be promptly, and apparently permanently, curative and now seldom delay surgical treatment.

TABLE 1. *Summary of Characteristic Features in 5 Cases of Low-Back Pain.*

Case No.	Age	Race	Sex	Body Build	Site of Lipoma	Duration of Pain	Effect of Local Infiltration with Procaine Hydrochloride	Effect of Surgical Excision	Surgical Specimen
	yr.								
1	53	W	F	Obese	Bilateral (right sacroiliac in 1946 and left sacroiliac in 1949)	1 to 2 wk.	No benefit	Prompt relief of pain	Right side (1946): herniated, pedunculated mass of normal fatty tissue. Left side (1949): nondiscrete normal fibrofatty tissue.
2	55	W	F	Obese	Bilateral (left sacroiliac in 1941 and right sacroiliac in 1945)	3 wk.	No benefit	Prompt relief of pain	Left side (1941): discrete lipoma. Right side (1945): discrete lipoma.
3	42	W	F	Markedly obese	Left lumbar region	22 yr.	No benefit	Prompt relief of pain	Nondiscrete, normal fibrofatty tissue
4	52	W	F	Obese	Left sacroiliac region	2 wk.	No benefit	Prompt relief of pain	Nondiscrete, normal fibrofatty tissue
5	69	W	M	Obese	Left sacroiliac region	4 yr.	Slight benefit	Prompt relief of pain	Well defined, nonpedunculated, necrotic fatty tissue

Summary and Conclusions

Painful, tender lobules of fat occur commonly in the sacroiliac regions, and recently have come in for increasing recognition as a cause of low-back pain. Obesity has been recognized as a common denominator in the majority of patients suffering from this condition. It is probable that fatty tissue herniates through an opening in the fascial plane, resulting in torsion and inflammatory changes, producing local tenderness of the nodule. Occasionally, inflammation may be present without actual herniation, but nodularity and tenderness are still apparent on examination. In other cases pain may be a prominent symptom without the observation of herniation or inflammation on surgical removal or pathological section of the specimen. Excision of the fatty tissue in this area has consistently resulted in prompt improvement of symptoms.

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TRACHEOESOPHAGEAL FISTULA UNASSOCIATED WITH ATRESIA OR STENOSIS: DIFFICULTIES IN DIAGNOSIS AND SUGGESTIONS FOR GREATER ACCURACY*

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CONGENITAL tracheoesophageal fistula without esophageal atresia has rarely been diagnosed in the first few days of life. This case reported below is presented to demonstrate that the condition does exist and can be diagnosed early and that detection of a small fistula may be enhanced by the use of an aqueous contrast medium instead of oil.

CASE REPORT

R. B. (B.H. 6386-50), the firstborn son of normal young parents, was transferred to the Children's Medical Service from another hospital at 48 hours of age with a diagnosis of "pneumonia and possible esophageal atresia." From the first feeding, 12 hours after birth, he had vomited all fluids (breast milk and water). On two occasions, immediately after the taking of nourishment, he had become cyanotic for several minutes.

On admission the infant was somewhat lethargic and was cyanotic about the mouth but did not appear to be in any respiratory distress. Significant findings on physical examination were a short, high-pitched systolic murmur heard to the left of the sternal border at the third intercostal space, and diminished resonance with reduction of breath sounds over the right-upper-lobe field anteriorly and posteriorly. Occasional inspiratory rales were heard over the same area, and many coarse inspiratory and expiratory rhonchi were heard throughout the chest, becoming markedly less prominent after nasopharyngeal suctioning.

The temperature was 100.2°F., the pulse 110, and the respirations 52.

X-ray examination of the chest in the anteroposterior and left lateral projections at 4:30 p.m. on January 23, 1950, showed the heart, trachea and mediastinal contents to be markedly retracted into the left hemithorax with both leaves of the diaphragm depressed and flattened bilaterally. Diffuse bronchopneumonic processes with areas of patchy atelectasis were noted throughout the right lung. The visible skeleton showed anomalous development of the 4th and 5th ribs on the left, posteriorly, as well as the bodies of the 12th dorsal and 1st lumbar vertebras (Fig. 1). These findings were believed compatible with aspiration pneumonia and atelectasis secondary to esophageal atresia.

Several hours later the patient was given ¼ ounce of 5 per cent glucose solution. Shortly afterward marked cyanosis of the mouth and extremities appeared, and he became restless; the respirations were shallow and rapid, though regular. Now there was dullness over both upper lobes, and coarse bubbling rales were audible in the right axilla and over both lung bases. Within 10 to 15 minutes the manifestations of acute respiratory embarrassment subsided, and an attempt was made to investigate the presence of a fistula.

At 8:30 p.m. fluoroscopic examination of the chest revealed that, as noted previously, the heart and mediastinal contents were retracted into the left hemithorax, both leaves of the diaphragm being depressed and flattened, with restriction of excursion bilaterally. A small catheter was passed into the stomach with no apparent difficulty. The catheter was withdrawn to the junction of the upper and middle thirds of the esophagus. In the supine position 2 cc. of Diodrast was introduced and was immediately seen to outline the right and left major bronchi and their ramifications, without regurgitation or aspiration. Some of the Diodrast entered the distal portion of the esophagus and stomach. Radiographic examination of the chest in the anteroposterior and lateral projections showed that the opaque mediums outlined the tracheobronchial tree, the distal portion of the esophagus and the stomach (Fig. 2). The diagnostic impression was tracheoesophageal fistula, without atresia of the esophagus.

Surgical consultants who saw the patient the same night hesitated to accept the presence of a tracheoesophageal fistula on the basis of the Diodrast studies. They believed that a sudden regurgitation and aspiration could have accounted for the presence of the contrast medium in the bronchial tree. Accordingly, they requested that the procedure be repeated with the use of Lipiodol. All oral intake was discontinued and fluids were administered subcutaneously.

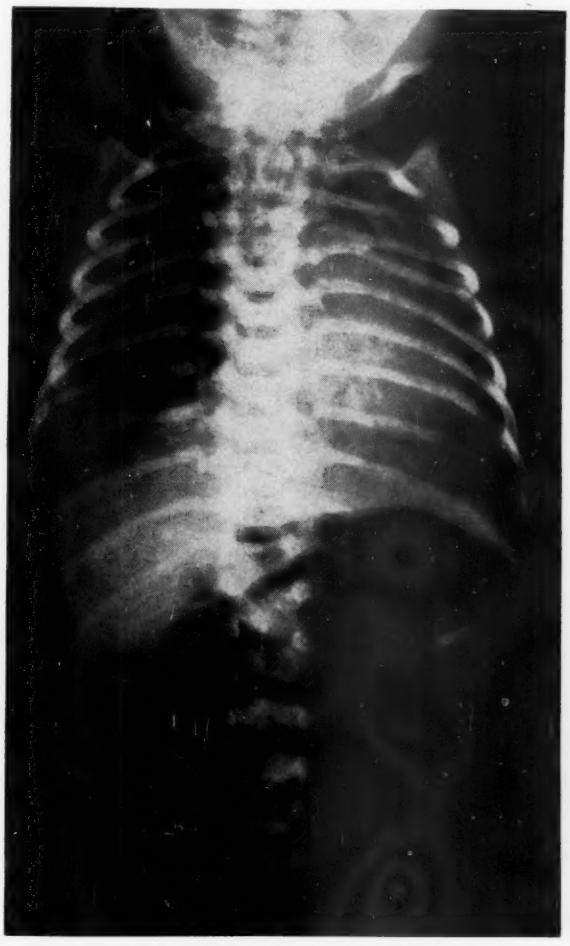

FIGURE 1. *X-Ray Film of the Chest, Showing Marked Retraction of the Heart, Trachea and Mediastinal Contents into the Left Hemithorax, with Bilateral Depression and Flattening of the Diaphragm.*

Diffuse bronchopneumonic processes, with areas of patchy atelectasis, are present throughout the right lung. The visible skeleton shows anomalous development of the fourth and fifth ribs on the left posteriorly, as well as the bodies of the twelfth dorsal and first lumbar vertebras.

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On the next morning at 8:30, under fluoroscopic control with the patient in the prone position, a catheter was passed into the stomach and then withdrawn to the level of the upper esophagus. Lipiodol was instilled, and the esophagus was seen to fill and distend, without evidence of atresia or constriction, the oil passing freely into the stomach. No oil entered the bronchial tree. Radiographic examination of the chest immediately afterward failed to reveal oil in the air passages. Incidentally, the pneumonic and atelectatic processes described previously showed evidence of extension, with involvement of the left base.

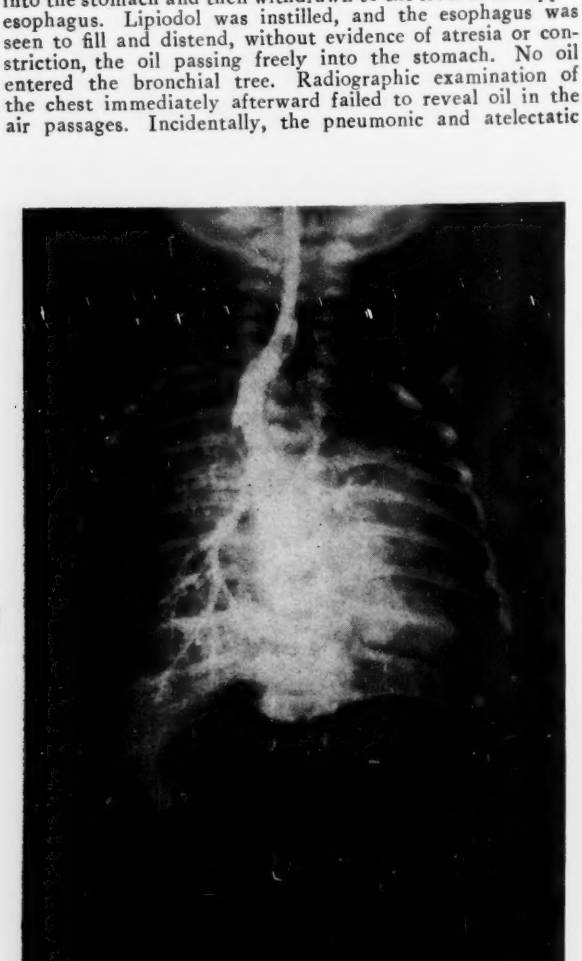

FIGURE 2. *X-Ray Film of the Chest, Showing Radio-Opaque Medium Outlining the Tracheobronchial Tree, the Distal Portion of the Esophagus and the Stomach.*

The catheter employed is seen reaching to the junction of the upper and middle thirds of the esophagus.

A bronchoscope was then passed, and with the trachea under direct visualization a solution of methylene blue was instilled into the esophagus. When no methylene blue was seen in the trachea it was concluded that probably no fistulous communication existed between the trachea and the esophagus, and since the patient seemed to be doing well on parenteral administration of fluids, it was considered wiser not to explore the chest at that time.

By the following morning the patient's condition had become critical. The respirations were shallow, rapid and irregular. Scattered rales were audible throughout both lung fields. The skin, especially over the outer aspects of the thighs and the left buttock, was noted to have a rubbery, hard consistence suggestive of sclerema. Meanwhile, the body temperature ranged between 97 and 95°F. Subcutaneous clyses and intravenous injection of fluids were continued in an attempt to maintain adequate hydration.

Several hours later the respirations suddenly stopped, but started again immediately after gentle intermittent thoracic pressure. However, the breathing was irregular and Cheyne-Stokes in character. The patient became more and more cyanotic, the peripheral pulses were absent, and the skin hardness had extended to involve all four extremities, the back and the face. Late in the same afternoon, 72 hours after admission, he died.

At autopsy the heart appeared slightly enlarged, weighing 20 gm. The right auricle and to a less degree the right ventricle appeared slightly enlarged compared to the left. There was a high interventricular-septum defect measuring 5 by 8 mm., and around it the endocardium was thickened and rather fibrotic. The aorta arose normally, and the pulmonic valve and the pulmonary artery appeared normal. The left myocardium was approximately 3 mm. in thickness. The right myocardium was slightly hypertrophied, measuring 4 mm. in thickness in the wall opposite the defect and approximately 2 mm. in the other areas.

FIGURE 3. *Post-Mortem Specimen of the Tracheobronchial Tree, Seen from the Esophageal Side.*

The arrow points to the fistulous opening.

The pleural surfaces of the lungs were smooth and glistening, but the lungs themselves showed a dark-red appearance, with a gross mottling. The bronchi were filled with a fairly thick, bloody, mucoid material, and the bronchial lymph nodes were normal. The right lung was almost completely consolidated, being of firm consistence and showing very little crepitation; on section, a firm, reddish-purple cut surface was revealed, closely resembling that of liver or spleen but showing some lobular variation in appearance. Scattered through the lung tissue and sometimes appearing on the surface were small white vesicles, less than 1 mm. in diam-

eter, which were filled with a thin, white material when they were cut into. The left lung showed both the same processes but to a less degree, with scattered areas in which there was a little consolidation.

On microscopical examination the bronchi contained inspissated foreign material. The walls and surrounding alveoli were infiltrated with many polymorphonuclear leukocytes and fibrin, and a few alveoli also contained the same aspirated material. Throughout, the entire architecture of the lung was distorted; in some areas all alveoli were filled with many well preserved red blood cells. The vessels were normal.

The esophagus was normal except that from the top of the larynx there was a mid-anterior longitudinal slit, 3 mm. in length, through which there was an opening into the trachea. The stomach was moderately filled with a mucoid, bloody material but was otherwise normal. The duodenum and small intestines were normal, except that 27 cm. from the ligament of Treitz there was a diverticulum, 4 cm. in length, with a normal mucosal lining, that opened freely into the intestine.

The trachea was normally formed except for the slit-like opening on its posterior surface that communicated with the esophagus (Fig. 3 and 4).

The anatomic diagnoses were congenital anomalies (tracheoesophageal fistula and interventricular-septum defect of the heart), aspiration pneumonia, hemorrhages in the lung, and sclerema, clinical and generalized.

Discussion

Four types of congenital tracheoesophageal anomalies are described. The most common is the condition in which an upper segment of the esophagus ends in a blind pouch at about the level of the bifurcation of the trachea or slightly above, and a lower segment from the stomach is connected to the trachea by a short fistulous tract. Much less common is the state in which both upper and lower esophageal segments are blind, neither being connected to the air passages. The third type is one in which the upper esophageal segment opens into the trachea and the lower segment is a blind pouch. The rarest condition, occurring in about 10 per cent of cases, is the one described in this report — that is, the communication of both upper and lower esophageal segments with the trachea or a bronchus through a large dehiscence in the party wall or a "small fistulous tract which may be very difficult to demonstrate."[1] Hence, it is erroneous to assume that because a catheter can be passed into the stomach, there is no fistula.

An extensive review of the literature has failed to unearth more than 1 case of tracheoesophageal fistula without esophageal atresia in which the patient survived early infancy and in which the congenital origin of the lesion was indisputable. It is not surprising that this should be so since practically all these patients die of aspiration and suffocation in the first few days of life. In a personal communication to Dr. Richmond McKinney, Dr. Chevalier Jackson wrote " . . . we suspected in some of the adult patients that the basis of the condition was congenital and that a thin, membranous layer of tissue had occluded it, enough to prevent entrance of swallowed food and liquids into the trachea until adult life; but we were never able to prove this."[2]

Hübner[3] reported a case of a double tracheoesophageal fistula with a normal esophagus in a twenty-six-year-old man who had had chronic aspiration pneumonia, bronchitis and bronchiectasis from childhood. He postulated a congenital origin but, in the absence of histologic sections, could not prove it.

Unless one is willing to accept Jackson's admittedly theoretical existence of a membrane during infancy and childhood, it is inconceivable that a tracheoesophageal fistula without esophageal atresia could fail to give characteristic symptoms during the earliest days of life. It is more likely that beyond the early months of life a fistula develops after perforation of the common wall by the passage of a foreign body or jagged food particles. The ingestion of a foreign body by a child may quite frequently go unreported or unnoticed, and the first symptoms may be those of choking or aspiration. In the older age group the cause may not be recognized as being neoplastic.

The sole case report of tracheoesophageal fistula without esophageal atresia that may be accepted as being congenital in origin is that of Imperatori.[4]

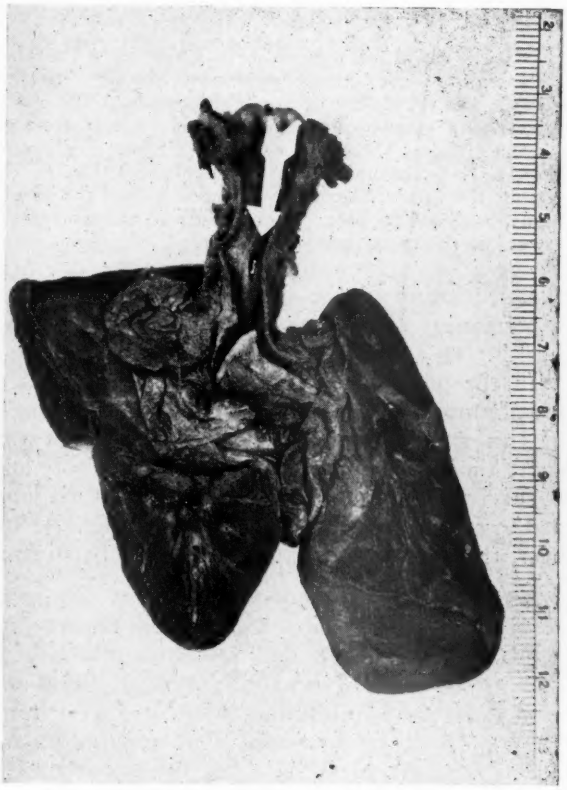

Figure 4. *Post-Mortem Specimen of the Tracheobronchial Tree, Seen from the Tracheal Side.*
The fistula is seen 0.5 cm. below the tip of the arrow.

Here the classic signs of choking, vomiting and cyanosis appeared in the first days of life. Pyloric stenosis was suspected, and the baby was operated on, with no apparent benefit. Throughout infancy and early childhood therapy was directed toward dilatation of the cardia by administration of antispasmodics, sedation and the use of mechanical dilators. Chronic pulmonary disease, retarded physical development and generally poor health persisted until the presence of a tracheoesophageal fistula was determined during the sixth year of life. At operation the fistula was found to be 1.3 cm. long and located in the party wall of the trachea and esophagus. Imperatori's description was as follows:

> It was slit-like in appearance and a trifle to the left of the sagittal plane. At the beginning of the act of swallowing it was closed, but as the larynx receded there was dilatation of the opening, which could be seen from the tracheal side. There was a partial diaphragm of muscle and mucous membrane on the esophageal side, so that when the fistula dilated the posterior wall of the esophagus could not be seen. The opening on the tracheal side was lower than on the esophageal side. . . .

Plastic closure of the fistula was performed, and a permanent cure obtained, with a return of good health.

In the ordinary situation, in which there is no membranous diaphragm to attenuate the dangers of this anomaly, death is certain within a very short time. Corrective surgery offers the only hope of survival, and the importance of correct diagnosis at the earliest possible moment is apparent. However, the fistulous communication may be so small or its course so devious as to impede the passage of a contrast medium of high viscosity such as Lipiodol. Under such circumstances an aqueous contrast medium like Diodrast offers a greater possibility of demonstrating the anomalous connection, as in the case reported above. A 35 per cent solution of Diodrast is not irritating to the bronchial mucosa and affords the additional advantage of being rapidly absorbed (within twenty-four hours), leaving no lasting residuum in the respiratory tree as the oily preparations do.

Summary

A case of congenital tracheoesophageal fistula without esophageal atresia is reported. The fistulous communication was so small that it permitted the passage only of Diodrast, a contrast medium of low viscosity. The use of a 35 per cent solution of Diodrast, which is not irritating to the bronchial mucosa and which is readily absorbed, is suggested as an aid to the early diagnosis of such conditions.

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EVALUATION OF THE PERITONEAL-BUTTON OPERATION FOR ASCITES*

Report of 17 Cases

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BOSTON

THE failure until recently of the nonsurgical management of ascites has led to several operative approaches to the problem. Omentopexy is no longer considered of value. Portacaval and splenorenal anastomoses[1, 2] are long and difficult operations, with a high mortality rate in patients with intractable ascites. The successful treatment of 5 out of 6 patients by the insertion of a glass Murphy button connecting the peritoneal cavity and the subcutaneous tissues of the abdominal wall was reported in 1946.[3] Previously sporadically employed, the button operation had been discarded because of consistent plugging of the lumen by the patient's omentum. The button recently devised had a flange on the peritoneal side to protect the lumen from obstruction. None of the 5 patients who survived the postoperative period required paracenteses for follow-up periods ranging from two to eleven months after operation.

Four reports of peritoneal-button insertions in small numbers of patients have appeared since 1946. In a series of 8 patients[4] the results were poor in 2, fair in 3 and excellent in 3. In another study[5] the results obtained in 6 patients were similar. There was 1 postoperative death; ascites returned within a month in 3 cases, and no paracenteses had been required during a three-month follow-up period in the other 2. One case of recurrence and 1 treated successfully by the additional step of removal of the anterior rectus sheath in order to enlarge the absorption area have been reported.[6] Post-mortem examinations in 2 patients whose ascites returned within a month of operation[7] revealed that a subcutaneous cystic space with a dense fibrous wall, lined with mesothelial cells and communicating through or around the button with the peritoneal cavity, had formed in both. It was suggested that the formation of such a cavity followed a predictable histologic sequence and that once it was formed the reabsorption of ascitic fluid was no faster than that from the peritoneal cavity as a whole.

Seventeen patients from the Medical Services of the Boston City Hospital and Mount Auburn Hospital, Cambridge, had buttons inserted during the years 1945 to 1947. The operations were performed by a number of different surgeons who were on service at the time. The technic was the same as that recently described.[3] In many cases a Leucite rather than glass button was used. One patient had a second button inserted on the opposite side a month after the first, and another had bilateral buttons inserted at one operation. The 14 patients from the Boston City Hospital were all followed closely by us during the preoperative and postoperative periods. The 3 other patients were seen by one of us during the follow-up period in the Out Patient Department of the Mount Auburn Hospital.

The essential data concerning each of the patients are presented in Table 1 and summarized below. The age and sex distribution was the same as that usually found in patients with cirrhosis of the liver with ascites.

DIAGNOSES

Twelve of the 17 patients had chronic alcoholism, with cirrhosis established by the usual clinical picture in all and at autopsy in 7. Two patients had post-necrotic cirrhosis, established by biopsy at operation in 1 and by autopsy in the other. In 1 case the cirrhosis was unclassified at autopsy, and 1 patient with chronic congestive heart failure and probable cirrhosis died at home. The final patient had a typical Chiari syndrome due to extension of a hypernephroma into the hepatic veins from the inferior vena cava.

PREOPERATIVE DURATION OF ILLNESS

Nine of the 17 patients required fewer than three paracenteses prior to operation. Five patients had from four to eight, and 3 patients from ten to eighteen paracenteses. The ascites had been present for less than a year in 12 cases and for one to three years in 5.

POSTOPERATIVE SURVIVAL

Five patients died within two weeks of the operation — 1 of pneumonia, congestive heart failure and uremia, and 4 in hepatic coma, precipitated by hematemesis in 2 and peritonitis in 2. The patient with Chiari's syndrome died of the metastatic carcinoma a month after operation. Four patients died of uncomplicated hepatic coma — 3 after three months, and 1 after twenty months. Two died of incarcerated umbilical hernias five and eight months after operation. One died three months after operation of a presumed reaction to intravenous adminis-

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tration of liver extract. Of the 4 remaining patients, 2 died at home of unknown cause, 1 each of subarachnoid hemorrhage and ruptured esophageal varices.

Recurrence of Ascites

All 11 of the patients who survived operation for more than a month had a return of significant ascites, in from two weeks to fourteen months — 7 within one month of operation. The reaccumulation was delayed for varying periods after the operation by the apparent transfer of fluid through the button from the peritoneal cavity to the subcutaneous spaces. This delay was insignificant in 6 patients (Cases 7, 8, 9, 10, 11 and 16 in Table 1) and paracentesis was necessary within a month. In 5 patients (Cases 12, 13, 14, 15 and 17 in Table 1) the delay was longer, ascites reappearing in three, six, one, fourteen and two months, respectively. The disability from the ascites and the need for paracentesis were distinctly lessened for these patients. One patient (Case 12) was definitely benefited, and in the eight months before she died of an incarcerated hernia paracentesis was unnecessary although on one occasion she had a spontaneous discharge of several liters of ascitic fluid through the umbilicus. The ascites of 1 patient (Case 14) returned after a month, but it soon disappeared without paracentesis and was absent during ten months of continued drinking. He then died of a subarachnoid hemorrhage, and at autopsy the button was found to be plugged by fibrin. One patient (Case 15) required no paracentesis for fourteen months, but his preoperative ascites was mild and he avoided alcohol and took a good diet throughout the postoperative period. Another patient (Case 17) required paracenteses in the third and fourth months after operation and had intermittent but mild ascites up to the time of his death four years after operation.

Post-Mortem Findings

Ten of the 17 patients were autopsied. No functioning buttons were found. Four of the buttons were plugged with fibrin, 2 by omentum, and 1 by an abscess. A pseudoperitoneal cavity as described above[7] was found in 5 cases and was assumed on clinical grounds to be present in a sixth. The two patients with bilateral buttons had bilateral pseudoperitoneal cavities. Three of the 5 patients whose result was considered good on clinical grounds were autopsied; the button was plugged by omentum in 2 and by fibrin in one.

Table 1. *Summary of Clinical and Pathological Data.*

Case No.	Diagnosis	Age	Sex	Preoperative Duration of Ascites	No. of Taps before Operation	Interval before Recurrence after Operation	No. of Taps after Operation
		yr.					
1	Chronic alcoholism and cirrhosis	63	M	2 mo.	1	?	0
2	Post-necrotic cirrhosis	56	M	1 mo.	1	?	0
3	Chronic alcoholism and cirrhosis	42	M	1 yr. (intermittent)	0	?	0
4	Chronic alcoholism and cirrhosis	39	F	5 mo.	1	5 days	0
5	Chronic alcoholism and cirrhosis	62	M	2 mo.	1	?	0
6	Chiari's syndrome (hypernephroma)	49	M	6 mo.	10	10 days	2
7	Chronic alcoholism and cirrhosis	56	M	1 mo.	2	1 mo.	1
8	Chronic alcoholism and cirrhosis	55	M	2 mo.	4	2 wk. 2 wk.	3 1
9	Cirrhosis, unclassified	57	F	2 mo.	1	1 mo.	2
10	Post-necrotic cirrhosis	54	M	4 mo.	1	1 mo.	3
11	Chronic alcoholism and cirrhosis	44	M	3 yr.	18	3 wk.	4+
12	Chronic alcoholism and cirrhosis	46	F	2 yr.	8	3 mo.	0
13	Cirrhosis, unclassified	63	F	1 yr.	6	6 mo.	1
14	Chronic alcoholism and cirrhosis	39	M	2 yr.	11	1 mo.	0
15	Chronic alcoholism and cirrhosis	60	M	2 mo.	0	14 mo.	5+
16	Chronic alcoholism and cirrhosis	50	M	10 wk.	4	1 mo.	6+
17	Chronic alcoholism and cirrhosis	77	M	5 mo.	4	2 mo.	2

Discussion

The high operative mortality, poor clinical results and complete lack of functioning buttons at autopsy mark the failure of the peritoneal-button operation for the relief of ascites in this series of 17 patients. The poor results may be partially attributable to the fact that some of the operations were done in a rush of enthusiasm before the patients were adequately prepared and that many of the patients continued to consume alcohol and to eat poorly after discharge. Nevertheless, even had the outcome been more satisfactory, the high incidence of pseudoperitoneal-cavity formation and the present availability of nonsurgical management of ascites militate against further trial of the procedure even under more ideal conditions.

Pseudoperitoneal cavities were found in almost all patients who lived long enough and whose buttons were not plugged by fibrin or omentum. The gross and histologic characteristics and the mechanism of formation of this subcutaneous pocket have been summarized above. Once such a cavity has formed, absorption of ascitic fluid from the subcutaneous tissue no longer occurs, and further paracenteses are made difficult by the pocketing of fluid and the postoperative adhesions.

The nonsurgical management of ascites consists of rigid restriction of sodium intake. Patients accumulating ascites usually excrete only small quantities of sodium in the urine regardless of the sodium intake.[8, 9] If the sodium intake is no more than the output, the accumulation of ascitic fluid stops. A nutritious diet, low enough in sodium to control formation of the ascites, has been described elsewhere.[10] Recently, the therapeutic effectiveness of rigid sodium restriction has been reported in 13 cases.[11] In spite of the previous need for many paracenteses, formation of ascites ceased in 12 patients; the thirteenth was unco-operative and did not tolerate the diet. On addition of sodium to the diet after a three months' period, ascites reappeared in only 8 of the 12, and in these it was again controlled by a return to the low-sodium diet. In another study,[12] 15 patients were treated with similar results. The patients became rapidly accustomed to the tastelessness of the diet and cooperated willingly once they realized that paracenteses were no longer necessary. After discharge they successfully maintained their low-sodium intakes at home. Several have been treated without admission to the hospital.

Since patients with cirrhosis are notoriously poor operative risks and since low-sodium food products are now more widely available, the dietary management of ascites is preferable to any surgical method so far described.

Summary

Seventeen patients with ascites were treated by the insertion into the abdominal wall of a modified Murphy button. Five died in the postoperative period, ascites promptly recurred in 7, and 5 appeared to be benefited for varying lengths of time.

No functioning buttons were found in the 10 autopsied patients. Subcutaneous pseudoperitoneal cavities formed after 6 of the button insertions.

The control of ascites by a low-salt diet is the best method of treatment now available.

Table 1 (*Concluded*).

Case No.	Interval between Operation and Death	Immediate Cause of Death	Post-Mortem Findings			Comment
			Pseudoperitoneal cavity	Plugged button	Peritonitis	
1	5 days	Uremia, pneumonia, congestive failure	—	—	—	No autopsy
2	5 days	Hematemesis and coma	—	—	—	Liver biopsy only
3	10 days	Peritonitis and coma	No	Yes (fibrin)	Yes	—
4	10 days	Peritonitis and coma	No	Yes (abscess)	Yes	—
5	14 days	Hematemesis and coma	—	—	—	No autopsy
6	1 mo.	Metastatic carcinoma	No	Yes (fibrin)	No	—
7	7 wk.	Coma	—	—	—	No autopsy
8	3 mo. 2 mo.	Coma	Yes Yes	Not described	Localized	Two buttons (1 mo. apart)
9	3 mo.	Coma	Yes (both)	Yes (both)	No	Two buttons (same operation)
10	3 mo.	Reaction to liver extract given intravenously	Yes	No (found under spleen)	No	—
11	5 mo.	Incarcerated umbilical hernia	Yes	No	No	—
12	8 mo.	Incarcerated umbilical hernia	No	Yes (fibrin)	No	Probably good result
13	8 mo.	Unknown (patient died at home)	—	—	—	No autopsy (probably good results)
14	10 mo.	Subarachnoid hemorrhage	No	Yes (omentum)	No	Probably good result
15	17 mo.	Bleeding esophageal varices	No	Yes (omentum)	No	Probably good results
16	20 mo.	Coma	Yes (clinical)	—	—	No autopsy
17	4 yr.	Unknown (patient died at home)	—	—	—	No autopsy (probably good result)

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MEDICAL PROGRESS

LABORATORY DIAGNOSIS OF POLYCYTHEMIA AND ANEMIA (Concluded)*

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BOSTON

In the following sections the various laboratory procedures to determine mechanism of red-cell destruction are outlined in order that the physician may study the problem of hemolytic anemias in an orderly fashion in view of present knowledge. These procedures have been found to be most useful as screening and specific tests. Although many other methods may be listed, those included herein have been used for several years and are considered most helpful. The more routine technics of enumerating blood values are not discussed.

8. Detection of Sickle-Cell Phenomenon

(*1*) *Principle*

Hahn and Gillespie[36] and others[18, 38-40] have shown that red blood cells from a patient with sickle-cell anemia or the sickle-cell trait change from a normal shape to the sickled form when the hemoglobin is reduced — that is, is caused to give up its oxygen. When resaturated with oxygen (or carbon monoxide) the sickled form of fresh blood reverts immediately to the normal form. Tests for the demonstration of the sickling phenomenon depend upon the removal of sufficient oxygen to produce the sickled shape. The usual procedure of incubating a drop of whole blood in a sealed preparation may be *unreliable* because the red cells may lose their ability to sickle[39] before sufficient oxygen has been used up by the cell metabolism.

When the sickled form is maintained in vitro for a considerable period, such as twenty-four hours, a large proportion of the cells cannot be reconverted to the normally shaped red cell.[39] By analogy, this may account for the irreversible sickled forms that are found in small numbers in well oxygenated peripheral blood in many patients with sickle-cell disease.

Tests in vitro for the sickle-cell phenomena have been performed by reducing the oxygen tension in the gas phase with which the blood is in equilibrium to 40 to 45 mm of mercury or less. This may be done by evacuation (vacuum pump)[40] or by displacement of oxygen with hydrogen, nitrous oxide, carbon dioxide or nitrogen.[36] Displacement of oxygen is enhanced by lowering the pH by the use of carbon dioxide. Reduction of the oxygen has been produced by adding leukocytes[40] or aerobic bacteria.[41] More recently, a variety of reducing substances have been used to produce sickling: sodium hydrosulfite,[32] hydrogen sulfide, cysteine and 2,3-dimercaptopropanol (BAL),[42] sodium metabisulfite ($Na_2S_2O_5$) and Cevalin,‖[31] and buffered dithionite ($Na_2S_2O_4$).[37] Two of these methods are given below.

(*2*) *Reduction of Blood by Equilibration with Carbon Dioxide*

(*a*) *Principle.* The oxygen can be removed by equilibration of a sample of blood with carbon dioxide, 100 per cent. However, the sickling so produced reverts promptly to the normal form if a film of blood is made and allowed to dry in air, a step that permits reoxygenation. The sickled form can be fixed by formalin in the following manner and examined in a wet preparation.[40]

(*b*) *Method.* The hemoglobin of a sample of 3 or 4 ml of blood is reduced by equilibration for 15 or 20 minutes with 100 per cent carbon dioxide gas in a 50-ml Erlenmeyer flask equipped with a two-hole stopper and inlet and outlet tubes. The gas is hydrated by bubbling it through water. The stopper is removed from the flask, and a micropipette is introduced immediately and beneath the surface of the blood; 0.1 to 0.5 ml of reduced blood is transferred immediately beneath the surface of a 2-ml or 3-ml sample of a solution consisting of one part of formalin (37 per cent) and nine parts of aqueous sodium chloride, 0.85 gm per 100 ml. The red cells are irreversibly fixed and may then be examined in a wet preparation under a cover glass.

(*c*) *Limitations and interpretation.* In wet preparations the cells in sickle-cell disease show a variety of changes. Characteristically, there are crescent forms, rounded forms with sharp projections and sickled shapes. These are readily distinguished from a crenated cell, which has short, spine-like projections and a rounded shape. If 10 per cent or more of the cells are sickled, the result is positive for the demonstration of the sickling phenomenon, but this result does not indicate whether the sickling

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis* (in press), by permission of the Harvard University Press.

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‖Buffered ascorbic acid and sodium metabisulfite, Eli Lilly and Company, Indianapolis, Indiana.

phenomenon is associated with anemia or only the trait. However, the observation may be repeated, or a reducing substance may be used to confirm the observation.

The foregoing method is a somewhat crude and indeterminate procedure for maintaining reduced hemoglobin since there is some opportunity for oxygen to gain access to the blood. However, the method will give reproducible results if precautions are taken to equilibrate the blood sample thoroughly, to avoid shaking the blood when the flask is unstoppered and to obtain a specimen from beneath the surface of the equilibrated sample.

Sherman[40] has reported that red cells from patients with sickle-cell anemia show the sickling phenomenon at a higher oxygen tension (40 to 50 mm of mercury) than those with the sickle-cell trait. There is no method, available clinically, to permit such a differentiation.

(3) Sodium Metabisulfite as a Reducing Agent

(a) Reagent. Aqueous sodium metabisulfite ($Na_2S_2O_5$), 2 gm per 100 ml, is made up fresh before use. For convenience, a 200-mg tablet* has been prepared, so that a fresh solution can be made each time by adding one tablet to 10 ml of water.

(b) Method. One or two drops of 2 per cent aqueous sodium metabisulfite are added to one drop of capillary or venous blood on a glass slide. After mixing, a coverglass is dropped onto the preparation, and the excess blood is expressed by gently pressing the coverglass with a piece of filter paper. This produces a wet preparation, which is thin enough to permit examination of individual cells. It is *not* necessary to seal the preparation. Observations should be made immediately and at intervals of fifteen and thirty minutes after preparation. If a negative result is obtained, a second preparation may be set up as a check on the procedure and blood sample. The solution of sodium metabisulfite, kept at 3 or 4°C, will remain effective for at least a week but gradually loses its activity.

(c) Interpretation. When a fresh solution is used, this method gives rapid and reproducible results, producing 10 to 75 per cent sickling within 15 minutes. Sterile defibrinated blood, kept at 3 or 4°C for more than a week, has given positive results. Normal blood treated in the same manner shows no sickling or injurious effects on the cells.

9. Determination of the Osmotic Fragility of Red Cells

(1) Principle

When red cells are introduced in hypotonic solutions of plasma, serum or sodium chloride, they imbibe water and swell until the spheroidal or critical volume is reached at which rupture occurs.[1, 7, 18, 22, 79] The spherical shape contains the maximum volume for the surface area of the cell, and any further increase in volume would lead to increase of the area of the membrane. The flat or thin cell, as seen in hypochromic anemia, has a decreased osmotic fragility (or an increased resistance) in hypotonic solutions because it can swell to a large extent in solutions of low tonicity before it reaches a spheroidal form and ruptures. However, a cell that is already spheroidal, as in congenital hemolytic jaundice, has an increased osmotic fragility (or a decreased resistance) in hypotonic solutions because it can swell to only a small extent before it reaches a spheroidal form and ruptures. If the osmotic fragility is determined quantitatively, the resultant summation curve indicates the distribution of cells of different geometric configuration — namely, the percentage of cells that have reached a spheroidal form and ruptured at different levels of hypotonicity. Representative curves are shown in Figure 5.

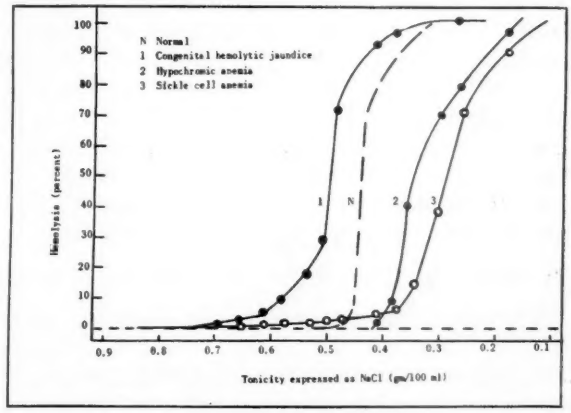

FIGURE 5. *Examples of Curves of Osmotic Fragility of Red Cells.*

Curve N. This curve of normal blood is approximately at the upper limit of normal (see Table 5).

Curve 1 — marked increase in osmotic fragility with asymmetric curve from a patient with congenital hemolytic jaundice and severe anemia before splenectomy.

Curve 2 — marked decrease in osmotic fragility associated with thin, flat cells in hypochromic anemia.

Curve 3 — mixed population in sickle-cell anemia. The majority of the cells are thin and flat with a decreased osmotic fragility. A small proportion show increased osmotic fragility.

A *semiquantitative procedure*, which is reproducible and does not require a colorimeter, is described by Daland and Worthley.[23] In this method, red cells are washed in aqueous sodium chloride, 0.85 gm per 100 ml, and resuspended at a hematocrit of 20 per cent, and 0.1-ml samples of the suspension are added to tubes containing 1.0 ml of the various concentrations of hypotonic salt solutions. After centrifugation of all the tubes the hemolysis of a patient's blood is compared to that of a normal sample by visual inspection of the amount of hemolysis in the supernatant fluid and the remaining unhemolyzed red cells.

*Available from Eli Lilly and Company, Indianapolis, Indiana.

A variety of procedures have been described for the determination of the osmotic fragility.[22, 23, 55, 122-124] Most quantitative methods require the use of a photoelectric-cell colorimeter, as in the technic described below. The procedure outlined below[55] is an arbitrary method that has the following features. The small dilution (1:11) permits the detection of small amounts of hemoglobin resulting from hemolysis of only 0.5 to 5 per cent of the red cells. The method is therefore sensitive to small amounts of hemolysis. Also, the small dilution enables the buffers of plasma and red cells to maintain the pH at that of the blood itself. In the hypotonic range, however, the addition of blood increases the tonicity, and the results are somewhat irregular for hemolysis above 75 per cent. However, the method is reproducible and is moderately rapid. Stock saline solutions can be made in large quantity once a year and kept stoppered at room temperature; they will remain uncontaminated if subsamples are poured from the stock solutions as needed.

(2) *Screening Test for Increased Osmotic Fragility*

A crude screening test for the detection of an increase in the osmotic fragility may be performed with only two concentrations of sodium chloride — namely, 0.85 and 0.50 gm per 100 ml. Samples of 0.1 ml of venous blood are added to 1.0 ml of the saline solutions described above, mixed and centrifuged. If hemolysis occurs in sodium chloride solution of 0.50 gm per 100 ml, the osmotic fragility of the red cells is probably increased and may be studied quantitatively, as by the method described below.

(3) *Quantitative Method for Osmotic Fragility*

A quantitative test[55] for osmotic fragility may be performed on freshly drawn venous blood containing balanced dry oxalate mixture as an anticoagulant. This can be done at a pH of 7.35 to 7.5,* by accurately measuring 0.1-ml samples of blood into a series of tubes each containing 1.0 ml of the following aqueous solutions of sodium chloride: hypertonic sodium chloride, 1.0 gm per 100 ml; isotonic sodium chloride, 0.85 gm per 100 ml; hypotonic sodium chloride, 0.80 to 0.10 gm per 100 ml, each tube differing by 0.04 gm per 100 ml; and distilled water. The samples are mixed and centrifuged, and 0.5 -ml samples of the supernatant solutions are diluted to 10 ml with distilled water, in Evelyn colorimeter tubes. One drop of concentrated ammonium hydroxide is added to each tube, the sample is mixed, and the hemoglobin is determined in an Evelyn colorimeter using filter No. 540.

The colorimetric values observed in the hypertonic saline solution are used as the *blank* and subtracted from each value observed in the hypotonic range to give a corrected figure for hemolysis. The percentage of hemolysis at each saline concentration is then calculated by dividing the corrected figure for hemolysis by the similarly corrected figure for complete hemolysis produced in distilled water. The curve of osmotic fragility is then plotted, with the hemolysis, in percentage, as the ordinate and the corrected tonicity of the hypotonic mixture as the abscissa.

(4) *Limitations and Interpretations*

Table 5 shows the osmotic fragility values for 30 normal subjects between the ages of seventeen and sixty-one. Representative curves are shown in Figures 5 and 6.

Biologically, the blood plasma is isotonic, equivalent to sodium chloride, 0.85 gm per 100 ml. Accordingly, an increase in the osmotic fragility may have no direct significance in relation to destruction of red cells, but it indicates the presence of spheroidal cells that may be removed selectively by and hemolyzed in the spleen. Diagnostically, the osmotic fragility is *increased* in certain cases of congenital and acquired hemolytic jaundice, in cells injured by heat, in certain drug intoxications and occasionally in a portion of the cell population of patients with sickle-cell anemia.[18, 21] The osmotic fragility of most of the population of red cells is *decreased* in conditions that are characterized by hypochromic, microcytic red cells, as in the anemia of iron deficiency and Cooley's anemia, and by the flat "target" cells of sickle-cell anemia.

TABLE 5. *Normal Osmotic Fragility Values for 30 Normal Subjects (pH of Blood, 7.35–7.5).*

VALUE	HEMOLYSIS OF 1 PER CENT	HEMOLYSIS OF 2.5 PER CENT	HEMOLYSIS OF 5 PER CENT	HEMOLYSIS OF 10 PER CENT	HEMOLYSIS OF 50 PER CENT	HEMOLYSIS OF 75 PER CENT	HEMOLYSIS OF 95 PER CENT
	TONICITY OF SODIUM CHLORIDE						
	gm/100 ml	*gm/100 ml*	*gm/100 ml*	*gm/100 ml*	*gm/100 ml*	*gm/100 ml*	*gm/100 ml*
Maximum	0.49	0.47	0.46	0.45	0.41	0.40	0.35
Minimum	0.42	0.40	0.38	0.37	0.33	0.31	0.21
Average	0.45	0.43	0.42	0.41	0.38	0.36	0.30

*The pH of 5 ml of blood, transferred to a bottle of 8-ml capacity containing dry oxalate mixture, will usually vary from 7.35 to 7.5 during the procedure of setting up the fragility test. Small amounts of carbon dioxide are lost. A decrease in pH produces progressive swelling of the red cell and increase in the osmotic fragility of the following approximate magnitude: for every decrease of 0.1 in pH the osmotic fragility increases by an increment of sodium chloride of 0.01 gm per 100 ml.

For example, if 1 per cent of red cells are hemolyzed at pH 7.5 in aqueous sodium chloride, 0.44 gm per 100 ml, a change in pH to 7.3 will be accompanied by an increase in osmotic fragility such that 1 per cent hemolysis will occur in aqueous sodium chloride, 0.46 gm per 100 ml.

10. Determination of Mechanical Fragility of Red Cells

(1) *Principle*

The susceptibility of red blood cells to destruction by mechanical trauma can be measured in an *arbitrary* manner as described below.[53, 55, 125] The mechanical fragility of the red cells is always increased when there is an increase in the osmotic fragility. However, in certain clinical conditions, the mechanical fragility may be increased although the osmotic fragility is normal.

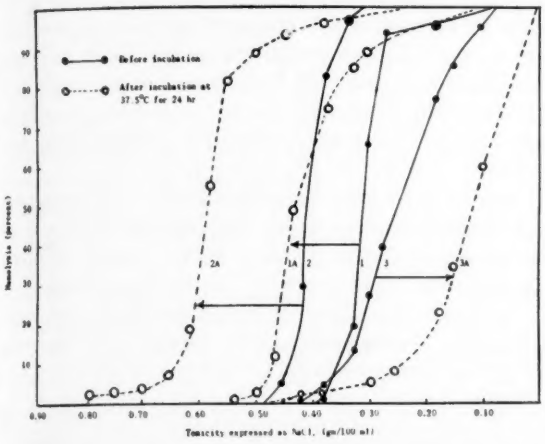

Figure 6. *Examples of the Effect of Incubation of Defibrinated Whole Blood on the Osmotic Fragility (All Samples Were Maintained under Sterile Conditions, and the pH Adjusted before and after Incubation to the Same Level — that is, pH 7.2 or 7.4).*

Curves 1 and 1A — normal subject. The mechanical fragility of the red cells, before incubation, was 3.6 per cent. There is a moderate increase in osmotic fragility on incubation.

Curves 2 and 2A — the trait of hereditary spherocytosis (congenital hemolytic jaundice) in a patient who showed no anemia or jaundice but a chronic reticulocytosis (count of 4 to 7 per cent). The mechanical fragility of the red cells, before incubation, was elevated significantly to 9.8 per cent. Note that the osmotic fragility of the unincubated sample is only slightly increased above the normal range (Table 5), a result that is indeterminate. The incubated sample, however, shows the striking symmetric increase in osmotic fragility that is characteristic for this disease.

Curves 3 and 3A — Cooley's anemia (see also Figure 4 for the same patient). The mechanical fragility of the red cells, before incubation, was 3.1. The osmotic fragility of the unincubated blood sample is decreased, consistent with the microcytic, hypochromic anemia (see Curve 2, Figure 5). After incubation the osmotic fragility is decreased further as occurs also in hypochromic anemia of iron deficiency. The significance of this change on incubation has not been defined.

(2) *Method*

An empirical method for the measurement of the mechanical fragility consists of the rotation of a small amount of blood in a 50-ml Erlenmeyer flask containing 10 glass beads of a uniform diameter of 4 mm. The flask is clamped in a position horizontal to the circumference of a vertical wheel. The center of the flask is located approximately 15-cm diameter from the axis of the wheel. The wheel is rotated at 30 rev/min (Fig. 7). The beads and blood are rotated around the maximum internal circumference of the flask. The rotating device may be placed in a thermostatically controlled box that is set at 37.5°C but this is not necessary and the procedure may be done at ordinary room temperatures.

Defibrinated blood or blood containing dry, balanced oxalate mixture may be used for the test. The hematocrit of 1.0 ml of blood is adjusted* to approximately 35 per cent, and 0.5 ml is introduced into a flask containing beads; the flask is stoppered and rotated for 90 minutes. The remainder is kept as the *unrotated control* sample, and 0.1-ml samples are introduced into test tubes containing 1 ml of aqueous sodium chloride, 1.25 gm per 100 ml (no osmotic hemolysis), and into 1 ml of distilled water (complete osmotic hemolysis). Duplicate amounts of 0.1 ml, from the *rotated sample*, are introduced into duplicate tubes containing 1.0 ml of aqueous sodium chloride, 1.25 gm. per 100 ml. The samples are mixed and centrifuged at 1000 rev/min for five minutes and 0.5 ml of the supernatant fluid is diluted with 9.5 ml of distilled water. The hemoglobin is determined with the Evelyn photoelectric-cell colorimeter.

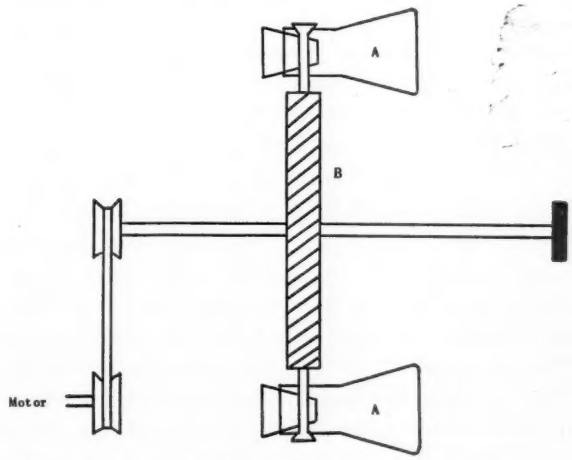

Figure 7. *Diagram of Apparatus for Determination of Mechanical Fragility of Red Cells.*

A — 50-ml Erlenmeyer flask, containing 0.5 ml of blood and 10 4-mm glass beads. B — Distance from axis to the center of the flask, or 15 cm. The speed of rotation is 30 rev/min.

The percentage of hemolysis due to trauma — that is, the mechanical fragility — is calculated as follows. If A is taken as representing the hemoglobin content of the supernatant fluid of the unrotated control sample in aqueous sodium chloride, 1.25 gm per 100 ml, B the hemoglobin content of the sample in 1 ml of distilled water, and C the average

*The percentage of cells destroyed varies directly with the concentration (hematocrit) of red cells in suspension.

hemoglobin content of the supernatant fluid of the rotated samples (duplicates) in 1 ml of aqueous sodium chloride, 1.25 gm per 100 ml, the percentage of hemolysis or mechanical fragility is (C–A)/(B–A). It is recommended that the mechanical fragility of a sample of normal blood be run for comparison with an unknown sample until the normal range of values is determined for the particular apparatus.

(3) Limitations and Interpretations

The normal values for human blood are between 1 and 5 per cent hemolysis with this empirical system. The mechanical fragility is increased in congenital hemolytic jaundice (7 to 12 per cent) in patients with the trait (no anemia) or with manifest anemia and in many cases of acquired hemolytic jaundice, whether the osmotic fragility is normal or increased. The mechanical fragility is markedly increased in cells that are firmly agglutinated or sickled.[125] When red cells are injured by heat there is a corresponding increase in both the osmotic and the mechanical fragilities.[53] The basis of an increase in mechanical fragility may be related to a decrease in the strength of the red-cell membrane, to increases in spheroidicity of the red cell or to firm agglutination of red cells. Biologically, an increase in mechanical fragility indicates an abnormality of the red cells and may be related to their increased destruction during circulation in vivo.

11. Diagnostic Value of Changes in Osmotic and Mechanical Fragilities

When samples of defibrinated blood from patients with congenital hemolytic jaundice are incubated in vitro under sterile conditions at 37°C for 24 hours with control of pH, there is a marked and uniform increase in osmotic and mechanical fragility that is greater than normal (Fig. 6). This has been uniformly observed and has served as a diagnostic aid because the osmotic fragility of unincubated blood may be *normal* in many cases of congenital hemolytic jaundice, either before or after splenectomy. Also, the degree of increase and the symmetric change in osmotic fragility have been characteristic of the red cell in congenital hemolytic jaundice, in contrast to other anemias, in which the red cells may show an *asymmetric* increase or an asymmetric *decrease* in osmotic fragility, as observed with microcytic, hypochromic red cells.

The mechanical fragility of incubated defibrinated blood increases in all cases, especially in congenital hemolytic jaundice. The degree of increase has not served as an aid in the diagnosis of a particular anemia but has indicated, broadly, the presence of an undefined abnormality of the red cells.

12. Donath–Landsteiner Reaction

(1) Principle

When the Donath–Landsteiner reaction is positive, it establishes the diagnosis of a disease called paroxysmal cold hemoglobinuria.[57-59] The test depends upon the demonstration of a hemolytic antibody in serum that has the following features. (i) The hemolysin is *not* active if the blood is kept at body temperature or, in most cases, at room temperature. (ii) Sensitization occurs only when the antibody has been fixed to red blood cells by chilling to 3 to 5°C in the presence of complement. (iii) Hemolysis occurs on subsequent warming of a previously chilled sample. (iv) Complement is required for hemolysis. (v) The hemolysin will hemolyze the patient's red cells and all normal cells (compatible blood groups). (vi) The patient's unsensitized red blood cells are normal.*

Tests in vivo may be performed to demonstrate intravascular hemolysis by chilling and then warming the finger — the Ehrlich test — or by chilling and warming of extremities — the Rosenbach test. The procedures, when positive, produce hemoglobinemia and hemoglobinuria. Details of the tests are given elsewhere.[3]

(2) Presumptive Donath–Landsteiner Test — A Screening Examination

(*a*) *Method.* The presumptive Donath–Landsteiner test is performed by the simple procedure of chilling a sample of 1 to 2 ml of whole ***defibrinated*** blood at 3 to 4°C in an ice bath for twenty minutes and then incubating it for one hour at 37.5°C. As *controls*, one sample of blood is centrifuged immediately, and another is incubated at 37.5°C for one hour without chilling. (***Precaution***: the blood should be kept warm to avoid sensitizing the cells at room temperature.)

(*b*) *Limitations and interpretation.* The possible results and their interpretations are listed below.

(i) *No hemolysis.* If no hemolysis occurs, the presumptive test is negative and excludes the disease paroxysmal cold hemoglobinuria (see also Table 6, Tubes 1, 2, 5 and 6). It is possible, but highly improbable, that a falsely negative result will occur from a decrease in complement in fresh serum or to anticomplementary action of the serum. Guinea-pig serum can be added as a source of complement, as shown in Table 6.

(ii) *Hemolysis in all tubes.* Approximately the same degree of hemolysis in all three tubes usually results from destruction of a moderate number of red cells by the mechanical trauma of defibrination of blood. It is of no clinical significance.

(iii) ***Hemolysis in both incubated samples.*** Hemolysis of a similar degree may occur in both the samples that are incubated, without hemolysis

*The direct Coombs test may be positive when the blood is cooled, even to room temperature.

occurring in the control sample, which is centrifuged immediately. This result may be obtained, rarely, without acidification of the serum, using a blood sample from a patient with paroxysmal nocturnal hemoglobinuria.[49] It may occur, rarely, with a serum hemolysin, effective at the normal pH of blood, that does *not* require chilling for hemolysis.[60]

(iv) *Hemolysis limited to the sample that is chilled and incubated.* If hemolysis occurs only in the sample that is chilled and incubated, this is a positive result indicating, presumptively, the presence of a cold hemolysin. The complete Donath–Landsteiner test should then be performed to establish the six diagnostic features outlined above.

An important cause of hemolysis, which is *not* produced by a cold hemolysin, is the mechanical destruction of red cells agglutinated by cold autohemagglutinins. Thus, the agitation of chilled blood containing cold agglutinins results in significant degrees of hemolysis that may be interpreted, erroneously, to result from a hemolysin. Gentle handling of the chilled sample will prevent mechanical hemolysis. Also, the red cells will appear agglutinated after chilling.

(3) *Complete Donath-Landsteiner Reaction*

The complete test will seldom be required because paroxysmal cold hemoglobinuria is an extremely rare disease. Accordingly, the demonstration of a negative presumptive test is usually all that is required. The method for the complete test is as follows:

(*a*) *Reagents*

(i) *Patient's serum* is derived from defibrinated venous blood, which is kept at 25°C or higher to prevent fixing of the hemolytic antibody to the red cells. Ideally, blood is taken with a syringe, warmed to 40°C, introduced into a tube warmed to 37.5°C in a water bath and centrifuged at this temperature in centrifuge cups filled with warmed water.

(ii) *Patient's red blood cells* are obtained as in (i), washed three times with an equal volume of aqueous sodium chloride, 0.85 gm per 100 ml, that is warmed to 37°C, and made to a 5 per cent suspension in saline solution. This procedure will remove cold autohemagglutinins.

(iii) *Normal serum* is obtained from defibrinated venous blood of the same blood group as the patient.

(iv) *Normal red blood cells* are prepared in 5 per cent suspension as in (ii).

(v) *Inactivated serum* is prepared by heating it for thirty minutes at 56°C to inactivate the complement.

(vi) *Guinea-pig serum* is used fresh or after preservation by freezing. Lyophilized guinea-pig serum occasionally is inactive for this test while showing full activity (complement) with sensitized sheep cells.

(*b*) *Method.* Combinations of 0.5-ml samples of the suspensions of red cells and of serums are made and treated as indicated in Table 6. The mixtures are then centrifuged, and the supernatant serums compared for hemolysis.

(*c*) *Limitations and interpretation.* The limitations and interpretations of results are similar to those given in Paragraph (2) (*b*) in this section.

(i) *Demonstration of a cold hemolysin.* A positive result, which is required to identify the presence of a cold hemolysin characteristic of paroxysmal cold hemoglobinuria, is shown in Table 6, tubes 5 and 6. If guinea-pig serum is added, the hemolysis in tubes 5 and 6 may be increased. If the cold hemolysin is thermostable, addition of guinea-pig serum to tubes 9 and 10 will re-establish hemolysis.

(ii) *Evidence that the patient's red cells are normal.* Unsensitized red cells from patients with paroxysmal cold hemoglobinuria are *normal* when examined morphologically, by the osmotic or mechanical fragility tests, or by the direct Coombs test.

(iii) *Positive Coombs test.* Red cells that have been sensitized but not hemolyzed by the cold hemolysin show agglutination in the direct Coombs test.[58] This observation may lead to the erroneous diagnosis of acquired hemolytic jaundice — a disease that is *not* associated with a *cold* hemolysin.

(iv) *Paroxysmal nocturnal hemoglobinuria.* The red cells from a patient with paroxysmal nocturnal hemoglobinuria may or may not be hemolyzed by *any* fresh compatible human serum at the normal pH of the blood (tubes 1, 3, 5 and 7 in Table 6). Added guinea-pig serum would enhance this hemolysis, but there would be no hemolysis in tubes 9 and 10. The hemolysis occurs only with the patient's red cells.

(v) *Cold autohemagglutinins.* The effect of a cold agglutinin is described above. Irregular hemolysis might occur in tubes 5, 6, 9 and 10 (see Section 18). Hemolysis in tubes 9 and 10, in the *absence of complement*, excludes the presence of a cold hemolysin and may be a clue to the presence of a cold agglutinin. Autohemagglutination by the cold agglutinin does *not* require serum complement.

13. Screening Test for Paroxysmal Nocturnal Hemoglobinuria, Hemolysins and Agglutinins

(*1*) *Principle*

It is remarkable that an acid pH of approximately 6.5 to 6.8 has been found necessary or optimum in four serum-red-cell reactions that are directly related to hemolytic anemias. These are as follows:

(*a*) *Hemolysis of patient's red cells in paroxysmal nocturnal hemoglobinuria.* The abnormal red cells are hemolyzed at an acid pH in normal serum.[49]

(*b*) *Acquired hemolytic jaundice.* Three different, but probably related, reactions either require or are

optimum at an acid pH of the serum from patients with acquired hemolytic jaundice.

(i) *Panagglutination at acid pH.* Gardner[70] has found in most cases of acquired hemolytic anemia that the serum agglutinates all normal red cells at an acid pH but not at an alkaline pH of 8.0.

(ii) *Indirect Coombs test at acid pH.* At an acid pH the indirect Coombs test usually is positive, but at pH 8.0 it usually is negative.[70]

(iii) *Hemolysis at acid pH.* Rarely, a hemolysin occurs that is active at pH 6.8 in producing hemolysis and sensitization of red cells but is not active at pH 8.0.[60]

A simplified *screening test* may be used for the detection or exclusion of these reactions based on the use of the patient's fresh serum, which is acidified to approximately pH 6.5 and incubated one hour at 37.5°C. If *no* abnormalities are detected, no more refined tests may be necessary. If abnormalities are found, the system involved is investigated in detail, as described in subsequent sections.

(2) *Method*

Approximately 5 ml of the patient's venous blood is defibrinated with beads. Plasma *cannot* be used because anticoagulants are anticomplementary. Approximately 4.5 ml of blood is centrifuged at 1000 rev/min for ten minutes to obtain 2.0 ml of serum. A sample of 0.1 ml of one-third normal hydrochloric acid is first placed in a small test tube; then 1.8 ml of serum is added and these reagents are mixed thoroughly. To make a suspension of approximately 1 or 2 per cent of red cells, 0.1 ml of the whole defibrinated blood is added and mixed. The pH of the final mixture will usually be approximately 6.5 to 6.8. The sample is then divided; 1 ml is centrifuged immediately as a control for color of the serum, and 1 ml is incubated in a water bath at 37.5°C for one hour. The incubated sample is first examined for agglutination; it is then centrifuged, and the supernatant fluid is inspected for hemolysis.

A sample of normal blood is treated in the same manner as a *control.*

(3) *Limitations, Interpretations and Further Examinations*

(a) *Hemolysis.* If hemolysis occurs in the incubated sample, it may be produced by any one of the three mechanisms outlined above — namely, paroxysmal nocturnal hemoglobinuria, acquired hemolytic jaundice and paroxysmal cold hemoglobinuria. No hemolysis should occur in the normal control. Rarely, hemolysis results in paroxysmal cold hemoglobinuria under these conditions when the red cells are sensitized at room temperature.[59]

(b) *Agglutination.* The above test is a crude one, designed only to detect the presence of agglutination. If no macroscopic agglutination is observed, 1 drop of incubated blood is placed on a glass slide, covered with a coverglass, and examined for microscopic agglutination. The presence of agglutination is abnormal and may result from a panagglutinin effective at an acid pH. However, the agglutination may also be caused by a cold autohemagglutinin or a warm autoagglutinin that is effective at room temperature.

(c) *Direct Coombs test at acid pH.* If *no agglutination* is observed microscopically, it is possible, however, that the red cells are sensitized by an antibody and that the sensitization will have been enhanced by incubation at acid pH. The Coombs test is performed by adding 1 drop of the incubated red-cell suspension (washed*) and 1 drop of immune antiglobulin serum, mixing and incubating at 37.5°C for one hour. Agglutination occurs in acquired hemolytic jaundice and erythroblastosis fetalis, and may occur when red cells are sensitized with but not hemolyzed by a cold hemolysin.

*The cell suspension must be washed to remove all traces of human serum that will neutralize the Coombs serum.[48]

TABLE 6. *Donath–Landsteiner Test.*

Tube No.	5 Per Cent Suspension Washed Red Cells, 0.5 Ml	Fresh Serum,* 0.5 Ml	Heated Serum, 0.5 Ml	Treatment of Mixtures	Hemolysis in Paroxysmal Cold Hemoglobinuria
1	P†	P		Incubate 1 hr at 37.5°C	0
2	C†	P			0
3	P	C			0
4	C	C			0
5	P	P		Chill 20 min. at 3°C, incubate 1 hr at 37.5°C	4+
6	C	P			4+
7	P	C			0
8	C	C			0
9	P		P‡	Chill 20 min. at 3°C, incubate 1 hr at 37.5°C	0
10	C		P‡		0
11	P		C		0
12	C		C		0

*Extra complement may be added by pipetting 0.1 ml of undiluted guinea-pig serum to each tube containing fresh human serum.

†P = Patient; C = Control.

‡In some but not all serums the cold hemolysin is destroyed or greatly decreased by heating. Therefore, a separate test using heated serum and *added complement* may give little or no hemolysis.

14. Hemolysis Test with Acidified Serum for Paroxysmal Nocturnal Hemoglobinuria

(1) Principle

When the hemolysis test with acidified serum, as described below, is positive, it establishes the diagnosis of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria; when the test is negative, it excludes the diagnosis.[49] The test depends upon the observation that the fundamental abnormality in this disease resides in the red cells. The following points are established by the complete test. (i) The patient's red cells are hemolyzed only by fresh human serum containing a thermolabile component of human serum. (ii) At the normal pH of blood, hemolysis occurs frequently, but not always, during incubation for one hour at 37.5°C. (iii) Hemolysis is always produced by increasing the acidity of serum within or beyond the physiologic range of variation in pH. (iv) Hemolysis is decreased or eliminated at an alkaline pH of 7.6 to 8.0 or above. (v) Destruction of complement by heat or other procedures eliminates the hemolysis in acidified serum. (vi) The addition of fresh guinea-pig serum, as a source of complement, does *not* re-establish the hemolysis for serum inactivated by heat. (vii) Any compatible, fresh, normal, human serum when acidified will hemolyze the patient's washed red cells. (viii) The patient's serum will *not* hemolyze compatible red cells from a normal subject — that is, there is no hemolysin in the patient's serum.

(2) Presumptive Tests

A presumptive test was described above (Section 13) and two others are described below. None of these tests are specific enough, however, to permit a diagnosis to be made, but all are adequate to exclude the diagnosis.

(a) Incubation at 37.5°C for acidification

(i) *Method.* A simple presumptive test may be performed by *incubating*, at 37.5°C, for six to twenty-four hours, a sample of 5 ml of *sterile* defibrinated (or clotted) blood from a normal subject as a control and from the patient, to observe hemolysis after six to twelve hours. Subsamples of 0.1 ml of defibrinated blood are centrifuged before incubation as controls on the hemolysis occurring during incubation. Usually, the pH will decrease sufficiently* — that is, pH 7.0 to 7.2 — during incubation to cause hemolysis in paroxysmal nocturnal hemoglobinuria.

(ii) *Interpretation and limitations.* No hemolysis should occur in the normal blood. If hemolysis occurs in the patient's blood the more complete tests should be performed (Paragraph 3 of this section and Section 17). Hemolysis of blood samples may occur in twenty-four hours of incubation in certain other hemolytic anemias, such as severe congenital hemolytic jaundice, and after thermal burns. In these two conditions there is no immunologic abnormality but a marked increase in the osmotic fragility of red cells.

*Lactic acid is formed.

(b) Use of carbon dioxide for acidification

(i) *Method.* A presumptive test may be performed promptly by acidifying defibrinated whole blood with carbon dioxide. By using carbon dioxide, 100 per cent, this test may be combined with the test for the sickle-cell phenomenon and performed as described in Section 8. The blood sample should be *defibrinated*, since anticoagulants are anticomplementary. Two additional controls may be performed with the presumptive test. A sample of the patient's blood may be equilibrated with room air or oxygen, 100 per cent, as a control on the change of pH and the mechanical trauma of the procedure. Equilibration with these gases produces a pH of about 7.9 to 8.1. Another control is the equilibration of normal defibrinated blood with carbon dioxide. This should not produce hemolysis from the acidification that is approximately pH 6.5. There may be slight hemolysis from the trauma of rotation. After equilibration, a sample is removed for sickle-cell† study and the remainder is poured out of the equilibrating vessel, incubated one hour at 37.5°C and centrifuged at the same time as an unequilibrated sample; the supernatant serums are then compared.

(ii) *Interpretation and limitations.* If the hemolysis of the acidified sample is the same as that of the controls, the test is negative. If the acidified sample is significantly hemolyzed, the test is presumptively positive, and the complete test should be performed. A small amount of hemolysis may occur from trauma during equilibration, which may be controlled as described above.

(3) Complete Test for Paroxysmal Nocturnal Hemoglobinuria

The complete test[49] is designed to demonstrate that the hemolytic reaction has the seven features described in Paragraph (1) of this section. It is a more demanding procedure.

(a) Reagents

(i) *Patient's serum* is derived from defibrinated venous blood.

(ii) *Patient's red cells* are washed three times with an equal volume of aqueous sodium chloride, 0.85 gm per 100 ml, and made to a 5 per cent suspension in saline solution.

(iii) *Normal serum* is derived from defibrinated venous blood of the *same* blood group as the patient.

†Only 100 per cent carbon dioxide can be used to deoxygenate red cell and produce sickling. However, the mixture of carbon dioxide, 10 per cent, and oxygen, 90 per cent, may be used to give a pH of blood of approximately 7.1 to 7.2. Because of its oxygen content, this mixture cannot be used for the sickle-cell test.

(iv) *Normal red cells* are treated as in Paragraph (ii).

(v) *Hydrochloric acid*, one third normal in distilled water.

(vi) *Fresh serum from a guinea pig*, serum undiluted.

(vii) *Acidified serum*: 1.9-ml samples of serum from the patient and the normal subject are measured into separate tubes and 0.1 ml of one-third N hydrochloric acid is added to each and mixed thoroughly, giving a pH of about 6.6.

(viii) *Heat-inactivated acidified serum*: 1.9-ml samples of both serums are heated for five minutes at 56°C to inactivate complement and, after cooling, 0.1 ml of one-third N hydrochloric acid is added to each and mixed thoroughly.

(ix) *Heat-inactivated acidified serum with added guinea-pig serum*: 1.5 ml samples of both serums are heated as in Paragraph (viii), and 0.1 ml of one-third N hydrochloric acid is added to each. Then, 0.4 ml of undiluted guinea-pig serum is added as a source of complement.

(*b*) *Method.* Samples of 0.5 ml of the suspensions of red cells are introduced into small test tubes (11 x 100 mm) as indicated in Table 7 and centrifuged, and the supernatant salt is removed with a micropipette. The salt must be removed since this hemolytic reaction is greatly decreased by dilution. Then 0.5-ml amounts of the reagents are introduced, as indicated in Table 7, mixed thoroughly, incubated in a water bath at 37.5°C for one hour and centrifuged, and the hemolysis is observed in the supernatant serums.

(*c*) *Interpretation.*

(i) *Paroxysmal nocturnal hemoglobinuria.* The hemolytic reaction, which is specific for paroxysmal nocturnal hemoglobinuria, is shown in Table 7 and establishes the features outlined in Paragraph (1) of this section.

(ii) *Paroxysmal cold hemoglobinuria.* Rare red cells are sensitized by the cold hemolysin at room temperature (see Section 12). This would produce hemolysis whenever the patient's active serum was used, irrespective of the red cells — tubes 1, 3, 9 and 11 in Table 7. Hemolysis would be inhibited by heating — tubes 5 and 13. In some cases the cold hemolysin in thermostable and hemolysis would be restored by guinea-pig serum — tubes 7 and 15. An acid pH of 6.5 to 6.8 does not inhibit hemolysis by the cold hemolysin.

(iii) *Hemolysin effective at acid pH.* With a hemolysin effective at acid pH, the hemolysis would occur whenever the patient's active and *acidified* serum was used — tubes 3 and 11. There might be no hemolysis or a slight amount in unacidified patient's serum — tubes 1 and 9. Heating would inhibit hemolysis — tubes 5 and 13; guinea-pig serum might restore hemolysis — tubes 7 and 15 — if the hemolysin is thermostable.

TABLE 7. *Hemolysis Test with Acidified Serum.*

Tube No.	Packed Red Cells* from 0.5 Ml of Suspension (5 Per Cent)	Unaltered Serum, 0.5 Ml	Acidified Serum, 0.5 Ml	Heated Acidified Serum, 0.5 Ml	Heated Serum Plus Guinea-Pig Serum, 0.5 Ml	Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (Per Cent)
1	P†	P				0–10
2	P	C†				0–10
3	P		P			2–30
4	P		C			2–30
5	P			P		0
6	P			C		0
7	P				P	0
8	P				C	0
9	C	P				0
10	C	C				0
11	C		P			0
12	C		C			0
13	C			P		0
14	C			C		0
15	C				P	0
16	C				C	0

*All salt is removed by centrifugation before adding serum to prevent dilution of the serum.
†P = Patient; C = Control.

15. Panagglutinin and Hemolysin, Effective at Acid pH

(*1*) *Principle*

Gardner[70] has demonstrated that most of the serums of patients with acquired hemolytic anemia will agglutinate the patient's own red cells and all normal cells when the mixture is acidified to approximately pH 6.5 to 6.8. The agglutination of such suspensions is reversed at pH 8.0. A screening test for this "acid agglutinin" is described in Section 13. The more detailed test devised by Gardner is discussed below. Dacie[60] has reported a hemolysin that is effective at an acid pH. The presence of this hemolysin will also be demonstrable by the same method (see also Section 17).

(2) *Method*

(a) Reagents

(i) *Patient's serum* is derived from clotted venous blood.

(ii) *Patient's red cells* are washed three times with an equal volume of aqueous sodium chloride, 0.85 gm per 100 ml, and made to a 10 per cent suspension in salt solution.

(iii) *Normal serum* is derived from clotted venous blood of the *same* blood group as the patient.

(iv) *Normal red cells* are treated as in Paragraph (ii).

(v) *Hydrochloric acid*, one third normal in distilled water.

(b) *Procedure.* The four possible combinations are made of the serum and red cells from the patient and a normal subject, shown as Series A, B, C, and D in Table 8. For each series, the range of pH is adjusted between approximately 6.1 and 8.0 by mixing thoroughly hydrochloric acid, saline solution and serum. The cell suspension is then added and mixed, and the pH may be checked. The dilution of serum is small and is maintained constant. The mixtures are incubated at 37.5°C for one hour and then centrifuged at 1000 rev/min for one minute and read for the presence of hemolysis. The tubes are then inverted gently and examined for macroscopic agglutination. If none is present, a drop of the mixture is examined microscopically for agglutination.

(c) *Limitations and interpretations*

(i) *Panagglutinin effective at acid pH.* Typical results are shown in Table 8, indicating the presence of a nonspecific panagglutinin that has a maximum effectiveness at approximately pH 6.5. It can further be demonstrated that an agglutinated sample will become unagglutinated if the pH is raised to 8.0.

(ii) *Hemolysin effective at acid pH.* A hemolysin may be demonstrated, rarely, that has a maximum effectiveness at pH 7.0. It is not hemolytic at pH 8.0.[60] Hemolysis would occur, therefore, in Series A and B at pH levels below 7.6.

(iii) *Paroxysmal nocturnal hemoglobinuria.* The red cells from a patient with paroxysmal nocturnal hemoglobinuria will be hemolyzed below pH 7.5 in Series B and D but *not* in Series A and C, containing normal red cells (see Section 14).

(iv) *Cold autohemagglutinins.* If cold agglutinins are present and active at room temperature, agglutination would be observed in Series A and B but would not be affected significantly by changes in pH.

TABLE 8. *Microscopical Agglutination Observed at Different Levels of pH for the Panagglutinin Effective at Acid pH*[70] *(Macroscopic Agglutination Is Frequently Present).*

Mixtures of Reagents					Series A		Series B		Series C		Series D	
One-third normal hydrochloric acid (ml)	Aqueous NaCl, 0.85 gm per 100 ml (ml)	Serum (ml)	10 per cent suspension of red cells (ml)	Expected pH of mixture	Tube no.	Agglutination patient's serum and normal red cells	Tube no.	Agglutination patient's serum and patient's red cells	Tube no.	Agglutination normal serum and normal red cells	Tube no.	Agglutination normal serum and patient's red cells
0.10	0.10	1.5	0.1	6.1	1	Trace to 1+	6	Same results as in Series A for corresponding pH	11	0	16	0
0.05	0.15	1.5	0.1	6.5	2	Usually 1+ to 4+ Rarely, trace	7		12	0	17	0
0.03	0.17	1.5	0.1	7.0	3	Usually 0 Rarely 1+ to 2+	8		13	0	18	0
0.02	0.18	1.5	0.1	7.5	4	Usually 0	9		14	0	19	0
0.00	0.20	1.5	0.1	8.0	5	0	10		15	0	20	0

16. Indirect Coombs Test at Acid pH in Acquired Hemolytic Jaundice

(1) *Principle*

Using serums from patients with acquired hemolytic jaundice, Gardner[70] has demonstrated a strong agglutination in the indirect* Coombs test at an acid pH of 6.5. At an alkaline pH of 8.0, the indirect Coombs test showed no agglutination in most cases. It has not been established, however, whether (i) the *panagglutinin* effective at an acid pH and (ii) the *antibody* producing agglutination in the indirect Coombs test at an acid pH are the same or different substances.

(2) *Method*

The same procedure is used as described in Section 15 and Table 5. After incubation the cells are washed in aqueous sodium chloride, 0.85 gm per 100 ml,

*The direct Coombs test shows agglutination of the patient's washed red cells in most cases of acquired hemolytic jaundice, as discussed elsewhere. In the indirect test *normal* red cells are used.

until *no* agglutination* remains. The Coombs test is then performed as described elsewhere.[68]

(*3*) *Limitations and Interpretations*

(i) *Agglutination at acid pH.* If agglutination in the indirect Coombs test occurs only with the cells treated at an acid pH, the results are characteristic of those observed in most cases of acquired hemolytic jaundice.[70] In a few cases agglutination occurs at pH 8.0.

17. Hemolysins — Hemolysin Effective at Acid pH

A variety of hemolysins have been described[61] in hemolytic anemia. Dacie[60] has demonstrated, in a case of acquired hemolytic jaundice, a hemolysin that had maximum effectiveness at pH 7.0 and had no hemolytic effect at pH 8.0. It was also demonstrated that normal red cells were sensitized by the hemolysin — the sensitization being maximum at pH 7.0 and absent at pH 8.0. A screening test and detailed procedure has already been described for the detection of a hemolysin effective at an acid pH. Other hemolysins will be readily detected by these procedures.

18. Cold and Warm Agglutinins

(*1*) *Principle*

Agglutinins are found in serums that produce maximum agglutination of red cells at 3 to 4°C and none at 37.5°C. These cold autohemagglutinins affect the patient's cells (autoagglutination) and all other human cells. Warm agglutinins produce maximum agglutination at 37.5°C and may show none at room temperature.

(*2*) *Method*

(*a*) *Reagents*

(i) *Patient's serum*† is derived from clotted whole blood or defibrinated blood.

(ii) *Normal red cells of Group O blood* are obtained from defibrinated blood or blood containing an anticoagulant. The cells are washed three times in an equal volume of aqueous sodium chloride, 0.85 gm per 100 ml, and made to a 1 per cent suspension in saline solution. Red cells of the same blood group as the patient's may be required at times.

(*b*) *Procedure.* The serum is used undiluted and after serial dilution with saline solution. Equal volumes of serum and red-cell suspension are mixed and incubated at different temperatures in water baths, as indicated in Table 9. The samples are read for macroscopic agglutination after gentle remixing. During the process of reading the temperature of the tubes must be maintained at that used in incubation by returning each tube promptly to the appropriate water bath (3 to 4°C, 25°C or 37.5°C).

Table 9. *Demonstration of Cold and Warm Agglutinins in Serial Dilutions of Serum (the Concentration of Agglutinin Is Reported As the Maximum Final Dilution of Serum That Gives 1+ Agglutination).*

Tube number	1	2	3	4	5	6	7	8	9	10	11	12
Saline solution (ml)	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0	0.5
Serum (ml)	0.5	0.5	Contents of tube 2 mixed and 0.5 ml transferred to tube 3. Serial dilution continued through tube 10, the contents of which are mixed and 0.5 ml transferred to tube 11.									0
Suspension of 1 to 2 per cent Red Cells (ml)	0.5	Throughout all tubes										
Final dilution of serum	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048	Control
Agglutination occurring with cold autohemagglutinin* under different conditions												
1 hr at 37.5°C	0	0	0	0	0	0	0	0	0	0	0	0
1 hr at 25°C	4+	2+	1+	0	0	0	0	0	0	0	0	0
1 hr at 3-4°C	4+	4+	4+	3+	2+	2+	+	+	0	0	0	0
24 hr at 3-4°C	4+	4+	4+	4+	3+	3+	2+	2+	+	+	0	0
Agglutination occurring with a warm agglutinin												
1 hr at 37.5°C	4+	3+	2+	+	±	0	0	0	0	0	0	0
1 hr at 25°C	2+	+	0	0	0	0	0	0	0	0	0	0

*In testing for cold agglutinins the temperature should be decreased from 37.5°C to lower figures since the agglutination at lower temperatures, such as 4°C, may not be readily reversed at higher temperature, such as 25°C.

(*3*) *Limitations and Interpretations*

(*a*) *Cold autohemagglutinins.* The origin of cold agglutinins is unknown. They develop, frequently in high titer, in at least a third of patients with atypical virus pneumonia[126] but are rarely associated with hemolytic anemia in this disease. Cold agglutinins are frequently found in low or moderate concentrations in patients with atypical hemolytic anemia and must be distinguished, therefore, from other antibodies found in this condition.

Rarely, intravascular hemolysis occurs with hemoglobinemia and with hemoglobinuria after chilling[71, 78] in patients with acquired hemolytic anemia. In these cases high concentration of cold agglutinins and an increase in the mechanical fragility of the red cells at *body* temperature have been observed. The Donath–Landsteiner test is negative.

The cold autohemagglutinins are nonspecific panagglutinins and should not be confused with the natural or immune isoagglutinins, which are specific for certain blood groups and may be most active in the cold. The isoagglutinins are *not* autoagglutinins.

*The cells may be rendered free of agglutination by incubating a 2-per cent suspension for 1 hour in normal serum at pH 8. The cells are then washed in saline solution.

†Plasma may be used, since complement is not necessary for the agglutination reaction.

(*b*) *Warm agglutinins.* Only rarely is an autoagglutinin found, usually in low titer, that has maximum effectiveness at body temperature. Usually, the warm agglutinins are natural or immune isoagglutinins that are group specific.

19. Tests Related to Hemoglobin Catabolism and Abnormal Forms of Hemoglobin

(*1*) *Principle*

The metabolism of bilirubin and the tests for bilirubin and its derivatives are not discussed here in detail. It can be re-emphasized, however, that patients with hemolytic anemia frequently show increased excretion of fecal urobilinogen with *normal* bilirubinemia. Also, a significant degree of destruction of red cells may occur with only small increases in one-minute bilirubin of the serum but with large increases in fecal urobilinogen. In manifest jaundice from increased blood destruction, the liver function may be remarkably normal with increased total bilirubin of the serum, acholuria and normal urobilinogen in the urine, but the fecal urobilinogen may be increased to five or ten times normal.

However, when *intravascular hemolysis* occurs without conversion of hemoglobin to bilirubin a series of events occurs as follows[127-131]; free hemoglobin appears in the plasma (hemoglobinemia) and is converted in part to methemalbumin, which is *not* excreted in the urine. If sufficient hemoglobin appears in the plasma, hemoglobin is excreted in the urine (hemoglobinuria). Hemoglobin in the urine may appear as oxyhemoglobin (red), reduced hemoglobin (purple) or methemoglobin (brown) or as mixtures. The tubules of the kidney convert some of the hemoglobin to hemosiderin, which also appears in the urine (hemosiderinuria). There may be only moderate increase in bilirubinemia and fecal urobilinogen associated with hemoglobinemia and hemoglobinuria. Occasionally, methemoglobin (MHb) and sulfhemoglobin (SHb) are observed in the intact red cell in patients with hemolytic anemia.[3, 80, 81, 103]

(*2*) *Determination of Hemoglobinemia*

(*a*) *Principle.* The presence of free hemoglobin in the plasma can be detected by the pink to red color. It can be measured quantitatively as described below using the benzidine method, or by the pyridine method,[132] which is not described here. The physiologic mechanism of clearance of plasma hemoglobin by the kidney has been well defined elsewhere.[128-130, 131] Below approximately 100 mg of hemoglobin per 100 ml of plasma, there may be no demonstrable hemoglobinuria, but there will be methemalbuminemia and hemosiderinuria. Above 100 mg of hemoglobin per 100 ml of plasma, hemoglobinuria occurs, and the plasma is cleared at an increasing rate as the level of hemoglobinemia increases.

(*b*) *Method for determination of hemoglobin in the plasma.* Hemoglobin and other heme compounds, such as methemalbumin, can be determined together but not separately by the quantitative benzidine method of Bing and Baker. Venous blood is collected with a syringe and needle that have been rinsed three times in aqueous sodium chloride, 0.85 mg per 100 ml. Nine parts of blood are added gently, with the needle removed, to aqueous sodium citrate, 3 gm per 100 ml. Only samples that are obtained from an uncomplicated venipuncture with a ready flow of blood are examined. The sample is mixed by gentle tilting of the tube and centrifuged *immediately* for ten minutes at 1000 rev/min; the plasma is removed with a micropipette. If all these precautions are taken the "normal" level of heme pigments in plasma is less than 5 mg per 100 ml.[49] For estimation of hemoglobin, samples of plasma are diluted to a known amount by adding distilled water until the color is a faint pink. Then 1.0 ml of the diluted plasma is added to 2 ml of benzidine solution* and 1.0 ml of 0.6 per cent hydrogen peroxide (prepared daily). The color developed in 1 hr is read after dilution with 20 ml of an aqueous solution of 20 per cent by volume of glacial acetic acid. The color can be measured in a visual colorimeter against a standard solution of hemoglobin treated as described for the unknown. To prepare a standard solution, a blood sample of known hemoglobin content is diluted to contain approximately 15 mg of hemoglobin per 100 ml of distilled water. The color can also be measured on the Evelyn photoelectric-cell colorimeter using filter No. 620.[133]

(*c*) *Limitations and interpretation.* Normal blood contains about 15,000 mg of hemoglobin per 100 ml. Accordingly, the above *precautions* against hemolysis by trauma are needed to have a "blank" or "normal" level in plasma of only 5 mg of hemoglobin or heme compounds per 100 ml. Methemalbumin gives the benzidine reaction and may be present in concentrations of 10 to 50 gm per 100 ml of plasma without evidence of hemoglobin itself. This occurs in paroxysmal nocturnal hemoglobinuria and after intravascular hemolysis in other conditions. The plasma appears golden in color. After severe hemolytic episodes, such as hemolytic transfusion reactions, the hemoglobin, free in the plasma, may increase to 500 or 1000 mg per 100 ml or more, giving a deep-red color. Levels of 50 to 250 mg of hemoglobin per 100 ml of plasma (measured as heme) occur frequently in paroxysmal nocturnal hemoglobinuria and in march hemoglobinuria.[49, 129]

(*3*) *Methemalbumin*

(*a*) *Principle.* Fairley[127] has shown that the hemoglobin is converted in the plasma to hematin,

*Benzidine solution: 1 gm of benzidine dihydrochloride
20 ml of glacial acetic acid
30 ml of distilled water
50 ml of 95 per cent ethyl alcohol

which is combined with serum albumin to form a golden to brown pigment, which is not excreted in the urine. Methemalbumin has been confused with methemoglobin and sulfhemoglobin, since each has a specific spectroscopic absorption in the region of 620 to 630 u. All three pigments react with benzidine. Methemalbumin is distinguished from other hemoglobin derivatives by the Shumm test.

(*b*) *Method of the Shumm test.*[127] Nine volumes of plasma are first covered with a layer of ether, and then 1 volume of a concentrated solution of ammonium sulfide is run in with a pipette and mixed. A positive reaction is indicated by the appearance of a hemochromogen with a sharply defined band at 558 u. This absorption band may be detected with a hand spectroscope.

(*c*) *Limitations and interpretation.* Apparently, methemalbumin in the plasma always follows an episode of hemoglobinemia and may be detected in decreasing concentration for a considerable number of days.[127] Accordingly, it may be sought for in patients suspected of having had intravascular hemolysis, such as a hemolytic transfusion reaction or anuria of undetermined origin. In chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, methemalbuminemia is apparently perpetual, once it is established, and is present for the life of the patient, which may be for years.

(*4*) *Hemosiderin*

(*a*) *Principle.* Whenever hemoglobin is passed by the glomerulus, the renal tubules ingest part of the hemoglobin[130] and convert the iron to a colloid sol of ferric iron, recognized as hemosiderin. Hemosiderin may be seen as discrete golden granules in the urinary sediments or may be present in casts. Hemosiderin can be detected with great ease and specificity as ferric sulfide by adding concentrated ammonium sulfide to a drop of urinary sediment; the golden granules turn black. Accordingly, this direct test, when positive, is usually a sign that the hemoglobin has passed into the renal tubules. Usually, this will result from hemoglobinemia and consequent hemoglobinuria. It is emphasized that hemosiderinuria may occur *without* manifest hemoglobinuria when the rate of clearance of hemoglobin is slow. In paroxysmal nocturnal hemoglobinuria there is *perpetual* hemosiderinuria. Hemosiderinuria is also described in hemochromatosis.

(*5*) *Methemoglobin and Sulfhemoglobin*

Methemoglobinemia occurs as a congenital anomaly with polycythemia.[3, 103] Also, transient methemoglobinemia and, occasionally, sulfhemoglobinemia occur after administration of certain drugs such as sulfanilamide,[3] acetanilid and certain oxidant compounds.[80, 81, 103] Rarely, hemolytic anemia follows intoxication by these compounds and may be severe with hemoglobinemia and hemoglobinuria. These abnormal pigments, which are in the red cell, are readily detected by the screening tests described by Evelyn and Malloy.[134]

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36481

PRESENTATION OF CASE

First admission. A fifty-two-year-old woman was admitted to the hospital because of long-standing heart disease, with increasing exertional dyspnea.

The patient stated that she had had "rheumatic heart disease for a long time." Three years prior to admission there had been a flare-up of the process, with onset of exertional dyspnea and the appearance of various cardiac arrhythmias. She had been treated as an office patient by her physician with digitalis and later with quinidine. However, she had been careless about taking the medications in recent weeks, and increasing exertional dyspnea had been noticed.

On physical examination there was slight dyspnea, but no cyanosis. The heart was enlarged moderately to the left at the apex and also slightly to the right. The rate ranged from 120 to 150. It was at first regular at 150, and then it became irregular with 3 or 4 regular beats and then a dropped beat. When the dropped beats occurred the rate usually dropped to around 120. Murmurs were heard but could not be timed because of the rapid rate. However, it was thought that both mitral and aortic valves were diseased. The lungs were clear, and there was no ankle edema.

The temperature and respirations were normal. The pulse varied from 80 to 120. The blood pressure was 90 systolic, 60 diastolic.

Laboratory studies on the urine and blood were normal. A roentgenogram of the heart showed considerable increase in size. It was triangular in shape, and there was a marked bulge in the region of the left auricle and pulmonary conus. The aorta was small, and the pulmonary artery prominent. The vessels in the pulmonary hilus were enlarged, and pulsations were visible. There was thought to be a small amount of fluid in the left costophrenic sinus. The pulsations of the heart were irregular but could be seen easily in the ventricles and less distinctly in the auricles. An electrocardiogram revealed auricular flutter with ventricular response varying from 2:1 to 3:1. There was widening of the QRS complex up to 0.10 second, probably early interventricular block. The T-waves were upright in Lead 1 and diphasic in Lead 2. A second electrocardiogram done five days later revealed auricular fibrillation with ectopic ventricular contractions and at times bigeminal rhythm. Following the second electrocardiogram the patient was redigitalized and put on a maintenance dose of 50 mg. (3/4 gr.) daily. She was discharged improved to continue taking digitalis.

Second admission (two and a half years later). For six months before admission she had sporadic rectal bleeding once or twice a month. There had been some increase in the severity of the dyspnea, which now occurred after slight exertion.

Physical examination revealed no marked change since the previous examination. There was a loud, blowing, apical, systolic murmur transmitted toward the sternum, an apical thrill and a heaving impulse. A few crackling rales were heard over the left lower lobe. The liver edge was felt 4 fingerbreadths below the costal margin. The blood pressure was 130 systolic, 90 diastolic.

Laboratory studies, including the blood count and prothrombin time, revealed no significant deviation from normal. The urine was normal except for a + test for albumin and 25 white cells per high-power field in the sediment. Barium-enema and proctoscopic examinations were reported as negative, and the patient was discharged with a diagnosis of rectal bleeding of undetermined origin.

Third admission (four years later). In the months just before admission there were an increase in severity of the exertional dyspnea, severe orthopnea and the development of paroxysmal nocturnal dyspnea. In the interval the patient had continued to live a semi-invalid existence. She had had occasional ankle edema, but this was relieved by injections of Salyrgan. She had no chest pain, cough or hemoptysis.

Physical examination revealed an apical thrill, a mitral systolic and diastolic rumble, an aortic systolic murmur and an accentuated pulmonic second sound. There were rales over the lung bases, and the liver was enlarged, with pulsation reaching to the umbilicus.

The temperature and respirations were normal, and the pulse and blood pressure showed no significant change from the previous examination.

The urine gave a ++ test for albumin, and the sediment contained 8 red cells and 5 white cells per high-power field. Examination of the blood disclosed a hemoglobin of 13.5 gm. and a white-cell count of 12,000, with a normal differential. The sedimentation rate was normal. An electrocardiogram showed auricular fibrillation, marked right-

axis deviation and variation in appearance of QRS complexes in different leads. The T waves were upright in Leads 1, CF_4 and CF_6, diphasic in Lead 2 and inverted in Leads 3 and CF_2. The ST segment was sagging in Lead 2. In a roentgenogram of the chest the heart was markedly increased in size as compared with the original films; the enlargement probably involved both auricles and the right ventricle (Fig. 1). The diameter of the heart was 21.7 cm., and that of the chest 25.5 cm. The pulmonary artery and its branches were markedly enlarged. The left main bronchus was markedly elevated by

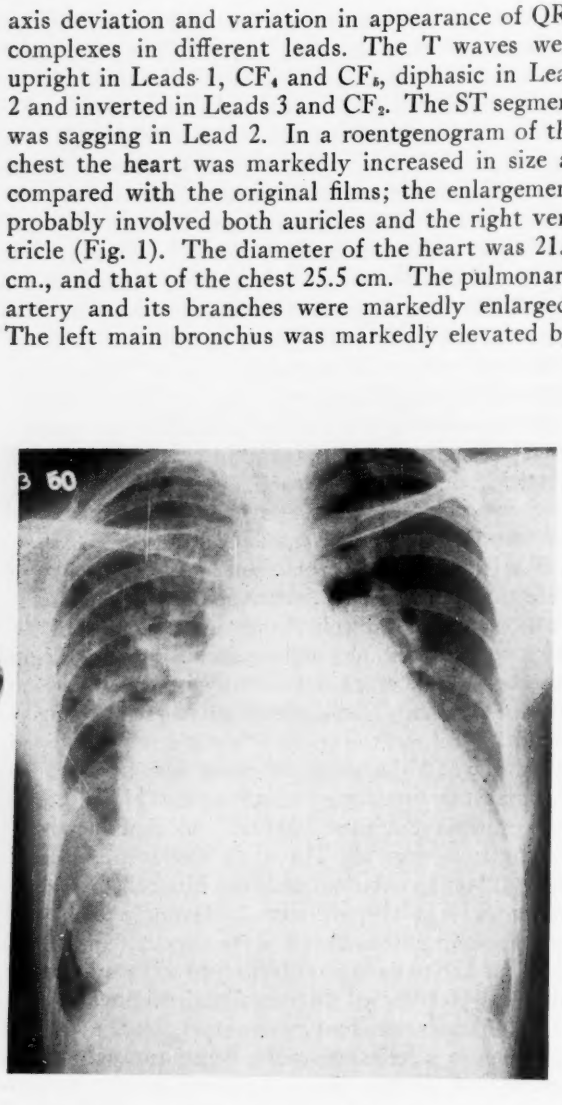

FIGURE 1. *Roentgenogram of the Chest, Showing Enlargement of the Right Ventricle and Both Auricles.*

the enlarged left auricle. Cardiac pulsations throughout were small. There was some fluid in both pleural cavities. There was calcification in the region of the mitral valve.

During the hospital stay five white-cell counts ranged from 12,000 to 22,000. She was discharged as improved after six weeks in the hospital.

Final admission (three years later). She stated that she had done fairly well on limited activity until a few months prior to admission. At that time she had had a sore throat and soon afterward became more dyspneic and orthopneic. Six days prior to admission, without known precipitating cause, she had become severely dyspneic even at rest. She had been able to sleep using only two pillows but now had to sit up all night.

Physical examination revealed a severely dyspneic woman sitting upright in bed. The heart was greatly enlarged, and there was a Grade III apical systolic murmur with a thrill and a Grade I diastolic rumble.

The temperature was 98.6°F., and the respirations 30. The blood pressure was 110 systolic, 80 diastolic.

The urine gave a + test for albumin, and the sediment contained occasional red cells. The sedimentation rate was 1 mm. in sixty minutes. An electrocardiogram revealed no significant change from the previous one.

On the evening of the second hospital day the patient fell while trying to go from the bed to a chair. Following this she complained of slight back pain, but physical examination revealed no change from the admission examination. After the doctor left she complained of more severe back pain but after receiving 75 mg. of Demerol she went to sleep with her head on the cardiac table. Early the next morning she suddenly slumped over and stopped breathing.

Differential Diagnosis

DR. CONGER WILLIAMS*: This is a long, involved story, which covers about thirteen years and from which it is quite obvious that this patient had heart disease. I have only to decide what kind of heart disease was present and what else, if anything, she had in addition. Three years before the first admission, nearly thirteen years before death, she had cardiac symptoms — namely, arrhythmias and dyspnea. It is quite possible that the dyspnea resulted from the cardiac arrhythmia, which could have been auricular flutter, fibrillation or auricular tachycardia. Nine years before death, at about the time of the first admission, she developed congestive heart failure, which was present more or less from then until death. Certainly, this clinical course suggests as much as anything else chronic rheumatic heart disease, probably mitral stenosis with auricular fibrillation and congestive failure. The fact that she had no clear-cut episodes of rheumatic fever at any time, of course, is not important in either establishing or eliminating a diagnosis of rheumatic heart disease. It is so easy to make this diagnosis that I wonder what surprise will be revealed at the end of the hour.

I should like to sum up the evidence for the diagnosis of rheumatic heart disease with mitral stenosis and possibly other lesions. The history of arrhythmias, fibrillations and flutter present for many years is compatible. At the time of the first admission there were murmurs present that could not be timed because of the heart rate; on the second admission a blowing systolic murmur was described; on the third admission there was an aortic systolic murmur and a mitral systolic and diastolic rumble; and on the fourth admission a Grade III systolic murmur and a Grade I diastolic rumble were heard. Although these murmurs were changing, that does not mean

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the valvular status had changed. The change may have been due to several things — to a rapid heart rate, to the degree of congestive heart failure or even to the skill of the examiner and the fact that probably four different physicians examined the patient. The x-ray findings of a triangular, enlarged heart shadow, an enlarged left pulmonary artery and left auricle, elevation of the left main bronchus and calcification of the mitral valve are consistent with a high grade of mitral stenosis. I do not anticipate much help from the electrocardiogram, which showed a pattern often seen in mitral stenosis but not specific for that lesion. The episode of sore throat occurring just before the final admission and followed by a great increase in congestive heart failure might of course mean active rheumatic fever without any of the so-called classic signs of the disease. The findings I have just mentioned are all consistent with the diagnosis of rheumatic heart disease with mitral stenosis.

Granting that this patient may have had mitral stenosis, what other valve lesions could have been present? Since an aortic murmur was described, possibly aortic-valve disease was present. Also, in a patient who has had severe peripheral congestion and a pulsating liver I should not be surprised to find involvement of the tricuspid valve. Where tricuspid-valve disease exists there is nearly always mitral stenosis as well.

What other cardiac diagnoses should I consider? The description of the pulsation of the pulmonary artery gave me a little pause. A pulsating pulmonary artery is rarely seen in mitral stenosis. Auricular septal defect and patent ductus arteriosus are the two lesions usually responsible for visible pulsation of the branches of the pulmonary artery. I wonder, therefore, if the patient had a small auricular septal defect in addition to mitral stenosis. Uncomplicated auricular septal defect is rarely associated with a large left auricle because the defect provides a left-to-right shunt between the auricles. Patent ductus arteriosus could have been present as a complication but certainly not as a primary lesion. The same statement is true of pulmonary stenosis and aortic stenosis of congenital origin. More esoteric diagnoses I shall skip. There was no evidence for them.

I cannot explain the rectal bleeding. An abdominal catastrophe can occur in the presence of auricular fibrillation (embolism), but it does not recur as this did without serious consequences. I do not have enough evidence to speculate further on the cause of the bleeding, and it was not present in later years.

A cardiac patient with this much peripheral congestion for many years is almost certain to have pulmonary emboli at some time. I expect that in the case under discussion the pathologist will report recent emboli or scars. It is reasonably certain that there was not a cor pulmonale from the recurrent pulmonary embolization.

There was nothing unusual in the final episode except that the back pain makes me somewhat suspicious. Among the conditions associated with sudden death in the presence of back pain is dissecting aneurysm. It does occur in the absence of hypertension, but there were no other findings to suggest it. Occasionally, also, a rupture of the aorta with retroperitoneal hemorrhage and dissection produces excruciating back pain and is compatible with life for as long as forty-eight hours. Renal infarcts are frequently present and many renal infarcts are silent. I am not told where the back pain was and know nothing about the kidney function, but apparently it was good, at least until the final episode.

My diagnoses are rheumatic heart disease with mitral stenosis, probably mitral regurgitation, aortic stenosis of slight degree, a question of tricuspid stenosis, old or recent pulmonary embolism and finally some surprise that I have not suspected.

Dr. Benjamin Castleman: Would you like to see the x-ray films now?

Dr. Williams: Yes; I should like to see them.

Dr. Stanley M. Wyman: The heart shadow shows great enlargement to both right and left (Fig. 1). There is probably enlargement of the right ventricle. A small amount of fluid is present in both pleural spaces; the main pulmonary artery and its major branches are tremendously enlarged. There is striking pulmonary congestion. I cannot exclude infarcts, but I cannot see any. The heart itself showed a very much diminished pulsation fluoroscopically. The pulsations of the main pulmonary artery and its main branches were not readily seen at the last entry. There was no suggestion of calcification in the heart and in particular no mitral-valve calcification.

Dr. Williams: If I had seen these x-ray films before I would have been tempted to add auricular septal defect to my diagnosis. The combination of this defect and mitral stenosis is known as Lutembacher's syndrome. I should like to ask Dr. Wyman if he ever sees this amount of congestion in the hilar region in uncomplicated mitral stenosis.

Dr. Wyman: It usually does not occur in uncomplicated mitral stenosis.

Dr. Williams: The clinical story is quite compatible with a diagnosis of Lutembacher's syndrome. Because of the size of the left auricle I believe that mitral stenosis was present and that the whole picture cannot be explained by auricular septal defect alone.

Clinical Diagnosis

Rheumatic heart disease with congestive failure.

Dr. Williams's Diagnoses

Rheumatic heart disease with mitral stenosis, ?aortic stenosis and ?tricuspid stenosis, probably complicated by auricular septal defect (Lutembacher's syndrome).

?Pulmonary embolism.

Anatomical Diagnoses

Congenital heart disease, interauricular septal defect.
Dilatation of right ventricle, severe.
Cirrhosis of liver, cardiac type, mild.

Pathological Discussion

Dr. Castleman: The heart showed a large interauricular septal defect (Fig. 2), which was the only anomaly and the only real pathological finding except for the tremendous dilatation of the right heart. The mitral valve was perfectly normal. The pulmonary artery was tremendously dilated, measuring 9 cm. in circumference at its origin. The right chamber formed most of the heart. The left ventricle was really small; its wall measured just the same as the right, 7 mm. We were unable to find any evidence of a mitral rheumatic condition.

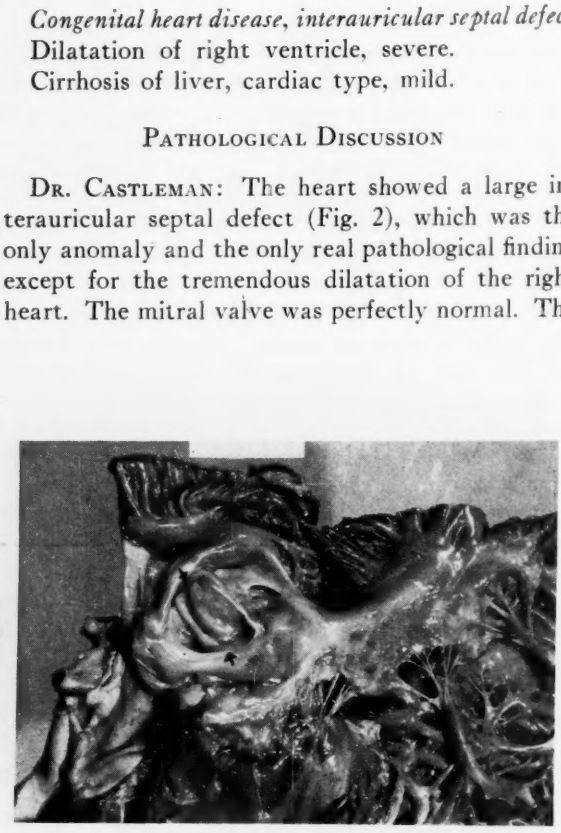

Figure 2. *Gross Appearance of the Heart. Arrows point to interauricular septal defect.*

Dr. Williams: What about the left auricle? Was it large, or was the elevation due to something else?

Dr. Castleman: The left auricle was only moderately large, but I do not believe the elevation was all due to the left auricle.

Dr. Wyman: I think this is simply the result of the left auricle's being pushed backward by the huge right ventricle.

Dr. Castleman: That is a more likely explanation. There was evidence of cardiac failure, and an early cardiac cirrhosis.

Dr. James H. Currens: It has been stated that an interauricular septal defect is not associated with dyspnea and pulmonary congestion; these findings tend to disprove that.

Dr. Williams: That was one of the points that inclined me to the diagnosis of mitral stenosis. Usually, the symptoms do not begin acutely with dyspnea, but perhaps the arrhythmia was responsible for this in the early stage.

Dr. Currens: I am now following a patient of about seventy-five with the same syndrome who has significant dyspnea.

Dr. Castleman: The heart itself weighed 575 gm., which is hypertrophy, to be sure, but the enlargement was due mostly to the marked dilatation, which filled the whole pericardial space. There was no space left for any fluid to accumulate, and there were no adhesions.

A Student: Were there any pulmonary thrombi?

Dr. Castleman: No thrombi, and no evidence of infarcts.

CASE 36482

Presentation of Case

A thirty-year-old woman was admitted to the hospital because of pain in the left gluteal region and groin.

Five years before entry, following the delivery of her first child, she had several episodes of lameness referred to the left sacroiliac region, associated with pain radiating into the left groin. These attacks were transitory, lasting two or three days, but occurred suddenly and frequently. The pain increased when she worked a great deal and was relieved by rest. It gradually subsided, and she was asymptomatic for about three years. After the birth of her second child similar attacks of pain recurred and were more severe and frequent. At this time she noted a limp on the left side. Again, the symptoms seemed to subside until approximately six months before admission when she was carrying her third child. During the last trimester she had almost constant discomfort and lameness in the left hip. She recalled that at the time of delivery she was unable to get her left leg up into the stirrup because of pain. Since that time she had limped almost constantly. Although the pain was intermittent, it was aggravated chiefly by walking and more recently she had begun to notice some pain at night. She described the leg as getting "stiff," either in the flexed or in the extended position, following which she had considerable discomfort getting it into a new position. She also noted considerable discomfort in getting from a sitting to a standing position or vice versa. When going upstairs she had to put her right leg up first although she could walk normally downstairs. She was able to cross her legs without discomfort, and to put on her shoes and stockings except in the standing position. Three months before admission she consulted an orthopedist whose findings were as follows:

The examination of the back was negative. The left leg was one-fourth inch shorter than the right. Straight-leg raising was 90° bilaterally. The reflexes were equal in both lower extremities, and there was no muscle weakness.

Examination of the hips revealed that the patient walked with a slight Trendelenburg limp. The Trendelenburg test was just positive. Motions of the hips were as follows: permanent flexion was 0 bilaterally; however, there was some limitation of hyperextension on the left. Flexion was 130° on the left and 140° on the right. Rotation in flexion: internal, left 15°, right 35°; external, left 0°, right 45°. Rotation in extension: internal, left 15°, right, 30°; external, left 25°, right 30°. Adduction on the left was 10° and on the right 25°. Abduction on the left was 10° and on the right 40°. There was moderate muscle guarding in motion of the left hip, and pain was elicited on the extremes of motion.

It was suggested that the patient carry on essentially as before, but to limit stair climbing as much as possible. A tuberculin test was negative, and the sedimentation rate normal. A roentgenogram

FIGURE 1.

of the left hip revealed very extensive cystic degeneration of both the acetabulum and femoral head together with spur formation about the margins of the femoral head (Fig. 1). There was marked narrowing of the joint space. She was to return two months later for further study. In the interval pain in the left hip persisted, and she felt unable to care for her three children.

There was no history of trauma. She had been very athletic until the onset of the symptoms five years previously. She had had scarlet fever at the age of eight years.

The physical examination was essentially the same as that recorded by the orthopedist two months before entry.

The temperature, pulse and respirations were normal.

The urine was normal. Examination of the blood disclosed a hemoglobin of 14.2 gm. and a white-cell count of 6500, with 67 per cent neutrophils. The sedimentation rate was 7 mm. in one hour. A blood Hinton test was negative.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES L. SHORT*: This is the story of a young woman with pain in the left hip on motion and muscular spasm going back probably five years. The onset and the first exacerbation after delivery are suggestive of the course in certain cases of rheumatoid arthritis. However, the final exacerbation occurred during pregnancy, which is rare in this disease. By physical examination the disease seemed localized to the left hip without evidence of referred pain from the spine as the explanation of the symptoms. There was no history of injury either recent or in childhood and nothing suggestive of childhood hip disease such as slipped epiphysis or Legg–Perthes disease that might have led to degenerative changes in adult life.

May I look at the x-ray films now? I think that the diagnosis will probably hinge on their interpretation.

DR. JAMES J. MCCORT: In the left hip we see marked narrowing of the joint space with small radiolucent areas in both the acetabulum and the head of the femur. The head appears to be slightly flattened, and in the lateral view there is spurring superiorly in the region of the acetabulum and also slight spurring at the superior margin of the femoral head (Fig. 1). The adjacent bone appears normal. There is one small break in the cortex at the head of the femur. The other joints — the sacroiliac, the right hip and symphysis pubis — show no abnormality.

DR. SHORT: There is no soft-tissue mass?

DR. MCCORT: No soft-tissue mass or soft-tissue calcification can be seen.

DR. SHORT: Is there any evidence of childhood hip disease?

DR. MCCORT: I do not believe so.

DR. SHORT: I shall discuss some of the conditions that might cause this picture. In the first place could the patient have had degenerative joint disease of a secondary variety? This is not exactly the x-ray picture for that. There is not enough condensation of the cortex and I believe there is too much destruction and cyst formation although in degenerative joint disease of the hip, small subcortical cysts are frequently found. I have already mentioned the lack of history and x-ray evidence of childhood hip disease or injury, the usual causes of degenerative joint disease at this early age. She had some hypertrophic spurring so that in a sense she had a hypertrophic reaction to the underlying disease, but I do not believe it was of primary importance.

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Rheumatoid arthritis is rarely confined to the hip alone without spinal or sacroiliac involvement. The exception lies in children. Here the process is often relatively mild and tends to clear without residua — that is, in the first attack. Exacerbation in pregnancy is also against this diagnosis. The patient had none of the constitutional symptoms of rheumatoid arthritis. The sedimentation rate was normal. The x-ray picture — chiefly lack of decalcification — is not that usually seen in rheumatoid arthritis.

One possibility that must be mentioned, although as far as I know it has never been described in the hip, is so-called pigmented villonodular synovitis or benign xanthomatous tumor. There is controversy about whether the process is inflammatory or neoplastic. It usually occurs in the knee. There may be subcortical destruction or loss of bone, but never destruction as extensive as this or joint narrowing. Furthermore, the absence of synovial swelling or soft-tissue mass by x-ray examination would be somewhat against this diagnosis. If she had this condition, this would certainly constitute a unique case, and one worthy of being reported.

Could she have had a septic joint in the past, — for example, after scarlet fever, which she had at the age of eight, — with residual destruction and hypertrophic change? In such a case there probably would be a definite history, perhaps more bony proliferation and probably ankylosis. However, I think an infectious process remains the most likely diagnosis, and I am referring to tuberculosis. I think Dr. McCort might agree that the x-ray picture is consistent with this diagnosis.

Dr. McCort: I would agree.

Dr. Short: This disease can produce a mild indolent course in the hip with exacerbations and remissions and absent constitutional symptoms. I have the impression that such a course is more frequent in the adult with hip tuberculosis than in a child. A negative tuberculin test and the normal sedimentation rate are certainly against this diagnosis. We are taught that a negative tuberculin test rules out bone and joint tuberculosis, but rarely proved cases have occurred. I should like to know the strength of the test employed. Finally, if this was tuberculosis, there should have been more than an even chance of demonstrating pulmonary disease in a chest film in this patient.

I should therefore like to make a diagnosis of active tuberculosis of the hip joint with secondary hypertrophic changes.

Dr. Joseph S. Barr: A chest film taken outside was reported as normal. Protein-precipitated-derivative tests for tuberculosis were in two strengths — both reported as negative.

Dr. Benjamin Castleman: Will you tell us the opinion before operation?

Dr. Barr: Here was a woman who had a history of monarticular hip disease over four or five years. We considered the various diagnoses Dr. Short has outlined. However, she had us very much puzzled. The negative tuberculin test was a considerable comfort to me because I really seriously suspected tuberculosis, and I am one of those who believe that if repeated tuberculin tests, up to 1:100 protein-precipitated derivative, are negative we can place a great deal of assurance on that. We considered rheumatoid arthritis, but she had the disease four years, no other joints were involved, and the sedimentation rate was absolutely normal — 7 mm. per hour.

Clinical Diagnosis

Arthritis, left hip, ?rheumatoid.

Dr. Short's Diagnosis

Tuberculosis, active, of hip joint.

Anatomical Diagnosis

Rheumatoid arthritis.

Pathological Discussion

Dr. Castleman: Dr. Barr, would you tell us what you found at operation?

Dr. Barr: On opening the capsule there was no excess fluid present. There was some injection and thickening of the synovia. On dislocation of the hip, the articular cartilage of the head of the femur was markedly eroded and almost completely destroyed in parts. The ligamentum teres was markedly thickened, with a thick layer of synovia surrounding it, and there was what appeared to be some granulation tissue in the fovea. There was marked offset of articular cartilage in the area of the fovea, the central area being depressed about 5 mm. The articular cartilage of the acetabulum was eroded in places. The cartilage of the head of the femur and the acetabulum and all of the capsule were

excised. A Vitallium cup was inserted. The hip then appeared to be quite stable, and there was an excellent range of motion in all directions.

I hesitated to do a cup arthoplasty on this hip, but the patient was averse to any consideration of arthrodesis unless it was absolutely necessary. We did not believe there was evidence of tuberculosis, and we did the cup arthroplasty.

DR. CASTLEMAN: The material removed at operation showed lymphocytic inflammatory reaction of the synovia that was quite consistent with rheumatoid arthritis.

DR. BARR: Following operation she developed acute synovitis of the left knee. The leg was in traction, and we wondered if the traction had anything to do with it, although the reaction was much more marked than one would expect from simple strain alone. In addition she developed aching in various other joints — the hands and wrists — and some limitation of the wrists several months after the operation. She had developed the clinical picture that appeared to be a full-blown rheumatoid arthritis.

I should like to make one more remark. We all think of rheumatoid arthritis as a polyarticular disease. In this case although we considered rheumatoid arthritis, we certainly had not made the diagnosis. I have another patient with a monarthritis and serosynovitis for twenty years on whom I finally operated. That too is now a proved case of rheumatoid arthritis. Following that operation she developed some other joint symptoms. I am becoming somewhat unwilling to operate in monarthritic cases, for I seem to spread the disease. I should like Dr. Short's opinion.

DR. SHORT: I can assure Dr. Barr that we have seen a number of cases of rheumatoid arthritis operated on without other joints becoming involved — at least the biopsy specimens were consistent with this diagnosis. I agree that we ought always to think of rheumatoid arthritis in monarticular joint disease, but, in disease confined to the hip, it is unusual for the patient to go five years without any evidence that other joints are involved. Even children at the end of five years usually show involvement of other joints.

DR. BARR: One question on therapy: this patient six months after operation had multiple subacute joints. Since she is unable to do anything in the way of exercise I am afraid both the knee and the hip joints are stiffening a good deal as a result of the progressive disease. Would you be willing to recommend one of the high-powered drugs or not?

DR. SHORT: That is a long story. If she is going downhill and getting worse in the face of adequate conservative therapy, I think that one of these drugs (ACTH or Cortisone) might be employed, but in that case she could not be expected to receive permanent improvement from one or more short courses. Plans should be made whereby she had the first series of treatments in the hospital and then would be carried along on three maintenance doses, more or less, of Cortisone a week on an ambulatory basis. That seems to be the only reasonable way of hoping for a more permanent, long-term result. However, not enough patients have been treated on this basis for us to say how long they can take the drug and how long they will continue improved without becoming refractory.

DR. CASTLEMAN: I might say, Dr. Short, that we have seen a villonodular synovitis in the hip that was sent to us from New Haven. It also had some of these cystic changes in the bone close by.

DR. SHORT: We have had cases with some subcortical decalcification, but they are rare.

NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-NINTH ANNIVERSARY

House of Delegates, September 10, 1950 (Continued)

The report of the Committee on Industrial Health was then presented, as follows:

This committee has continued its activity during the past year in the development and promotion of industrial health among New Hampshire industries and among other groups of workers in the state. These activities of the Committee may be briefly summarized as follows:

The chairman of the Committee attended the Tenth Annual Congress on Industrial Health sponsored by the Council on Industrial Health, American Medical Association, which was held in New York City, February 20-21, 1950. At this conference many excellent papers were presented on the values, benefits and achievements to both industrial management and employees through industrial medical services. Responsibilities of industrial medicine and its relation to other practicing physicians were discussed in detail. It was pointed out that industrial medicine throughout the United States has made tremendous progress during the past ten years, not only in the prevention of occupational diseases and in the development of better work conditions but also in the improvement of the health of industrial workers through periodic physical examinations, proper job placement and emergency treatment for injuries.

The chairman also attended a conference on industrial medicine sponsored by the Committee on Industrial Health of the Massachusetts Medical Society, which was held on December 14, 1949, in Boston. At this conference, papers were presented and discussed on such subjects as: organization and administration of an industrial medical department; industrial medicine and the aging worker; relationship of occupation to health; and other subjects pertinent to the industrial medical programs in New Hampshire.

The Committee continued to give its co-operation to the Division of Industrial Hygiene, New Hampshire State Health Department, in its activities relating to the protection of the health of industrial workers. Among these activities were the chest x-ray program of workers in industrial plants, periodic chest x-ray examination of workers exposed to potential silicosis hazards and the control of toxic chemicals to which industrial workers are exposed.

In view of the increased use of the new organic phosphates for insecticides in greenhouses and among agricultural workers, the committee co-operated with the New Hampshire State Health Department in the preparation of an information circular on the toxicology, treatment and prevention of poisoning from parathion (hexaethyltetraphosphate) and tetraethylthiophosphate. This circular was sent to all physicians in New Hampshire. In addition, a circular prepared by one of the manufacturers of parathion (Monsanto Chemical Company) was sent to greenhouse operators, which gave information of protective devices and safeguards necessary in the use of these materials.

Several other information circulars on the toxicity and safe use of the common organic solvents as used in industrial plants are in the process of preparation and will be printed and distributed to industrial management and industrial physicians in New Hampshire.

The Committee is continuing its effort to obtain factual information on the cost and benefits of industrial medical programs among plants in New Hampshire. It is expected that within the next year such information will be ready for publication.

The Committee believes that there is a tremendous amount of work that needs to be done if industrial medical and health programs in New Hampshire are to be equal with those that are now being conducted in other states. While the majority of the larger plants in New Hampshire have medical and health programs there is a great need for such programs in the smaller plants. It is possible that through further study several small plants may be able to join together for the purpose of providing an industrial medical and health program for their employees. If such a plan could be developed, it would provide many benefits to both management and the employees in this state.

It is recommended that the Committee continue and increase its activity in the stimulation of the development of industrial medical programs in the plants in New Hampshire and continue to provide information to industrial management on policies and procedures for such programs. In addition, the Committee should continue to work with the Department of Health in the preparation and dissemination of educational material designed to acquaint industrial officials with potentially harmful chemicals used in industrial processes and with preventive methods to use to safeguard against industrial poisonings.

JOHN C. ECKELS
ROBERT FLANDERS
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CHARLES F. KEELEY
ROBERT W. HOLMES
JOHN S. WHEELER
DANIEL F. McCOOEY

Dr. Brown moved that the report of the Committee on Industrial Health be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The report of the Committee on Maternal Health and Infant Welfare was then presented, as follows:

The Committee has conducted an annual study of maternal deaths, stillbirths and early infant deaths for sixteen years. This, the sixteenth report, marks the lowest maternal death rate in all the years of study. The Committee feels most amply paid for the effort and work put forth in collecting the data and appraising each case as reported by physicians throughout the State, because of this gratifying and steady decline in maternal deaths.

The Committee includes in the report a listing of stillbirths by cause, no particular study having been made in each case. Stillbirths are listed by county of birth and by place of birth (home or hospital). There is also a listing by cause of infant deaths under one year. It is the Committee's hope that an exhaustive study of infant deaths will be conducted by the pediatricians of the State at some future time, since it is the belief that such a study falls best within the province of the pediatrician, rather than the obstetrician.

Attached to this report are Tables 1-7, showing maternal deaths for 1949 by cause, place of occurrence and groups, emphasizing the responsibility in the conduct of the case, and also a list of maternal death rates per 1000 live births by years since 1933.

For purposes of clarity, the method of conducting this study of maternal deaths for the calendar year 1949 was the same as in the past. The co-operation of the State Department of Health was obtained through use of personnel in the Divisions of Maternal and Child Health and Vital Statistics. In order that the Committee may review the cases reported without prejudice and as objectively as possible, all information relative to the identity of the physician, patient, hospital or locality is obtained by the State Department of Health, acting as the Committee's agent, and is kept in strictest confidence. When the data are compiled and prepared for study, the Committee meets and discusses, appraises and evaluates each case from facts available to it. In some cases additional information must be obtained through contact with the physician. After final classification of the case by the Committee, a letter containing the Committee's comments is sent to the reporting physician by the agent. It is the Committee's

hope that such a procedure may prove helpful in the conduct of future cases presenting similar problems. Results in the steady decline of maternal deaths over the years seem to bear out this hope.

This report is made possible only through the co-operation of physicians furnishing as full and descriptive information and facts as possible. Failure to reach a proper decision may be due to improper or inadequate information pertinent to the case.

This year the data submitted by physicians were of the very best quality. In most cases there were copious notes from hospital records, laboratory data, some autopsy reports and notes of the consultant. It was gratifying to note that more consultations were held, particularly when operative procedures were indicated.

All cases of maternal deaths are reviewed through the Division of Vital Statistics of the State Department of Health, where death records are received and filed.

Maternal Deaths

In 1949 there were only 8 maternal deaths. The number of live births was 12,229 — giving a maternal death rate of 0.65 per 1000 live births. Ten maternal death records were actually submitted to the Committee, but after a study of the facts, 2 of them were determined as being from nonmaternal causes and were excluded. This study has assisted the Division of Vital Statistics immeasurably in determining the true cause of death in these cases through the Committee's follow-up report.

The record of this all-time low maternal death rate is exceedingly gratifying. In 1948 there were 14 deaths with a rate of 1.1 per 1000 live births. In one year this rate has been reduced almost to an irreducible minimum, with the number of maternal deaths cut nearly in half. Despite this excellent record, the work of the Committee should continue in order to encourage continued good standards.

The table of causes of maternal deaths is the most interesting of any past years. There are but three large categories of causes for death. The amazing fact was that the patients in 5 of the 8 maternal deaths bled to death either before or shortly after delivery. Mention of placenta praevia was made in 1, retention of the placenta in 2, abruptio placentae in 1 and premature separation of the placenta in the other 5 cases.

There were 2 cases of toxemia in 1949. Both patients received adequate and prompt treatment, a fact to emphasize since in the past the greatest problem seemed to be lack of knowledge on the part of many physicians of what constituted adequate handling of toxemia with or without convulsions. Eclampsia or the toxemias were the chief cause of maternal deaths up through 1947. In the 1942 maternal death report the Committee included a very thorough discussion of the treatment of toxemias, and repeated it almost every year since that time in some abbreviated form.

One patient was reported to have died of an acute coronary occlusion at her home, about thirteen days after delivery of an anencephalic fetus. Labor was induced by rupture of the membranes, and the delivery progressed without incident. Consultation was obtained before labor was induced, and as soon as the physician made the diagnosis of an anencephalic fetus on x-ray examination. Treatment was adequate, and the patient had an uneventful post-partum course. After the patient had returned home she called the doctor because of pains in the right kidney region. The temperature was normal, and the pains responded to medication. Suddenly, just thirteen days after delivery, the patient developed an acute chest pain and died while returning from the bathroom. The Committee agrees with the physician's diagnosis that death was due to an embolus, probably through the vena cava from the pelvic veins. No autopsy was performed because the physician reported the family could not afford the cost. The Committee believes that it is most regrettable that costs of autopsies are such as to interfere with performing one, especially in cases such as this, in which the cause of death was difficult to determine and in which an autopsy would have established an accurate cause of death.

The greatest number of patients in the 1949 series of patients died from hemorrhage. The most striking case to which the Committee wishes to call attention is as follows:

A forty-one-year-old gravida II, para I, was seen early in pregnancy and had excellent prenatal care and enjoyed an entirely uneventful prenatal course. Blood, urine and all laboratory findings were negative during pregnancy. The blood group was A, Rh+. The patient entered the hospital in spontaneous labor of three hours' duration before admission. There was no vaginal bleeding, and there was no episode of acute abdominal pain. After a seven-hour normal labor an uneventful low-forceps delivery was done at full dilatation of the cervix. The membranes had ruptured spontaneously one hour before delivery. The placenta followed immediately after the fetus and showed evidence of extensive intra-partum separation. Thirty minutes after delivery, the patient went into extreme shock due to blood loss, and throughout the entire post-partum course the blood characteristically failed to clot at any time. Massive transfusions, calcium and vitamin K were of no avail. Hysterectomy was done after consultation about three and a half hours post partum, in an effort to stop the hemorrhage, but the patient continued to bleed from the cervical stump. She bled from the abdominal wound and episiotomy and from the gums. A total of 5000 cc. of whole blood was given, but still she bled. She died a few hours after the hysterectomy.

Cases of this type have become recognized very recently, and the Committee wishes to call attention to this series of patients who bleed during the puerperium. It has been described as a pathologic process initiated by massive placental separation, which causes the release of fibrinolytic substance into the general circulation. This produces a rapid afibrinogenemia. In the above case a sample of blood taken from the vein showed absolutely no fibrinogen.

In the other patients who died of hemorrhage there is less evidence of what the blood picture was before death, but in every one of the series the hemorrhage followed a placenta praevia, premature separation of the placenta or retained placenta. In 2 of these cases there was evidence of kidney damage or suspected toxemia in the prenatal period.

Two patients did not show much external bleeding after delivery and baffled the physicians as to why the patient should have gone into shock. However, in each case hemorrhages had occurred into the uterine wall, or, as in 1 of the cases, a massive hemorrhage from the stomach occurred, since the patient vomited huge quantities of blood just before death.

Vaginal packing was inserted before delivery because of bleeding in 1 case, and the Committee wishes to state that this practice is not to be condoned.

In the further discussion of this type of case in which uncontrollable hemorrhage occurs, it should be pointed out that the fibrinogen level of the blood reaches a very low level or may actually be absent (as in the case described above). Under such circumstances, the giving of whole blood has been found to be practically useless, since no clotting power of the blood is present. As fast as the whole blood is transfused into the veins of the patient, it will continue to run out through the uterus or from some other tissue. In this series most of the bleeding was into the uterine wall or from the uterus.

This whole picture is not as yet completely clear, but it is thought that there is a fibrinolysin present in the amniotic fluid and in necrotic decidua. This is very frequently associated with partial detachment of the placenta either with or without toxemia.

Since this lysin, if it comes into contact with the maternal circulation (as may occur when the placenta starts to detach after the birth of the fetus, or in cases in which there has been a partial detachment previous to birth), causes a marked lowering of the fibrinogen of the mother's blood, it is thought advisable to rupture the membranes early in cases in which this condition is suspected, so that there may not be too much amniotic fluid present when the placenta starts to detach in the third stage of labor.

It is interesting to note that all but one of the fetuses in this series were stillborn. Sometimes the ante-partum death of the fetus may be due to a partial separation of the placenta, and in all such cases of ante-partum death, an afibrinogenemia should be suspected, as it also should

in cases in which a steady flow of blood begins after the delivery of the placenta.

It should be noted that the laboratory determination of the fibrinogen content of the maternal blood is an extremely difficult procedure and probably not desirable in any small hospital. It should suffice, however, to draw a test tube partly full of the maternal blood, and if it does not clot in a reasonable length of time, it is safe to assume that the fibrinogen level is low or completely absent. The Committee suggests that at the onset of labor, when the fetus is known to be dead, the coagulability of the maternal blood be determined.

In many of these cases, the fibrinogen is quickly pushed from a low level of perhaps around 100 to an absolute zero. This may be due to the fact that sufficient amniotic fluid has come in contact with the maternal sinuses as the placenta starts to detach, with the resultant introduction into the maternal circulation of a large amount of the lysin that is present in the amniotic fluid. Hence the advisability of early rupture of the membranes.

The Committee wishes to stress the fact that if the maternal blood has no power to clot, it is useless to transfuse with whole blood. In such cases fibrinogen should be given immediately. If fibrinogen is not available, it may or may not be true that dried plasma should be used. The fibrinogen content of liquid plasma is known to deteriorate very rapidly. Whether or not the fibrinogen of dried plasma remains sufficiently active to be of use is still undetermined.

It is agreed that whole blood should be given also, but after the fibrinogen is given and the hemorrhage controlled. It is believed that one unit of fibrinogen should be sufficient to restore the normal fibrinogen level in the maternal blood within about half an hour. The decline and disappearance of fibrinogen in the maternal blood is rapid and dramatic, but temporary, if control measures as described above are instituted and prove effective. There is much that needs to be learned about this peculiar phenomenon that is not currently known.

It is strongly urged that all hospitals with a maternity service keep fibrinogen on hand at all times for possible emergency use in these cases. It is also urged that contact be made with Dr. Louis K. Diamond, at the Children's Hospital in Boston, for the purpose of obtaining a supply of fibrinogen. This is a dried substance and may be mixed for use by dissolving in 250 cc. of either physiologic saline or 5 per cent glucose solution.

The Committee further classifies maternal deaths for purposes of the study, into four groups, as follows: *Group I*, those in which the patient was at fault because of failure to obtain prenatal care, neglect or refusal of treatment and so forth; *Group II*, those in which obstetric treatment was apparently inadequate; *Group III*, those that were apparently unavoidable; and *Group IV*, those with insufficient data and undetermined.

A table of these groupings follows in the report. It should be noted here that there were no cases classified in Group II.

Comments and Recommendations

It is seldom that the Committee receives comments of commendation from within or without the State. It is gratifying that few if any comments of condemnation have followed the reports over the years. By way of interest to the medical profession, the Committee wishes to quote in part at least from a letter received from Dr. Edwin Daily, director of Health Services of the Children's Bureau, as follows:

> Knowing of the many, many hours of work you and your Committee members have given to this task over a long period of years, I wanted all of you to know that I believe this is a labor of great reward. It is my belief that the remarkable decline in maternal mortality during the past decade or two is due more to these painstaking case studies by physicians than to any other single factor. The appraisal of all preventable factors and the steps taken each year to meet these problems have been most successful.
>
> I do hope you will continue your work, and if time permits, begin with the pediatricians some intensive studies of the late fetal and early infant deaths. The results of such studies, I am confident, would be equally rewarding.

The Committee is most grateful for these comments and suggestions. The Committee hopes to continue the study of maternal deaths, but wishes to confine itself to obstetrics and to some degree to delve further into problems resulting in stillbirths. It recommends to the Child Health Committee of the New Hampshire Medical Society or to the pediatricians, or both, that plans be made for them to explore causes of death in the newborn and in early infancy.

In its capacity as technical advisory committee to the State Department of Health on Maternity and Infancy, the Committee reviewed and approved the use of the confidential detachable birth record now in use in the Department of Health. This has proved most effective as a means of locating and assisting physicians to obtain correction of congenital defects and other handicaps. Co-operation of physicians in its use is urged.

Further comments of the Committee based on 1949 maternal deaths are as follows:

It is recommended that in cases in which an adherent placenta occurs, the use of 1 cc. of Pituitrin be given at two-hour intervals accompanied by the Crêdé maneuver only at the time Pituitrin is given. This should be tried before any attempt at manual removal is made. Manual removal is unjustifiable under twelve hours unless there is excessive or uncontrollable hemorrhage. The Crêdé maneuver should be done with the greatest of care, the obstetrician remembering always to exert only an anteroposterior force and never pressure downward. Too early Crêdé maneuvers should be avoided. It should be remembered that the third stage of labor is the most dangerous stage of all. No placenta should be delivered unless the fingers of one hand are between the fundus and the symphysis pubis.

The Committee believes that emphasis should again be placed upon the problem of placenta praevia. It wishes to repeat the recommendation that placenta praevias in a primipara should always be delivered by cesarean section, and that all complete placenta praevias, whether in a multipara or a primipara, should be delivered by section.

The Committee disapproves in general of the use of vaginal packing or cervical packs to control hemorrhage. Danger of masking the bleeding into the uterus and of subsequent infection is feared by such methods. Vaginal packing should never be done ante partum.

When there is not much post-partum external bleeding, but if the fetus is delivered dead, an abruptio placentae should be suspected rather than placenta praevia.

The Committee regrets that the cost of performing an autopsy need be given as an excuse that one is not done. Autopsies should be made available to those who cannot afford to pay, and an autopsy is necessary in obscure cases in order to establish the correct cause of death. Autopsies should be performed if possible on every maternal death.

The Committee urges all hospitals having a maternity service to obtain fibrinogen to be available at all times, for use in cases in which noncoagulability of the blood is apparent.

The Committee wishes to emphasize and re-emphasize the necessity of proper and prompt diagnosis and immediate treatment of women who hemorrhage or who show signs of shock after or during delivery, whether the delivery is spontaneous or operative. External or vaginal bleeding is frequently scant and shock is out of proportion to the bleeding. The most important causes of hemorrhage in the puerperium are a partially separated placenta, retained cotyledons of a removed placenta, a retained placenta, lower-segment tears, ruptured uterus, atony of the uterus, fibromas, ruptured vaginal varicosities, inverted uterus and afibrinogenemia (noncoagulability of the blood).

The series of maternal deaths in 1949 illustrates the urgent necessity for thorough diagnosis and appraisal of the situation where hemorrhage is suspected or apparent.

The Committee wishes to thank all physicians and hospitals who so ably and thoroughly prepared the necessary information so pertinent to make this study possible. Suggestions or comments from physicians as to the future conduct of this study would be gratefully received by the Committee.

The Committee wishes to acknowledge with appreciation the co-operation received from members of the New Hampshire State Health Department, particularly those connected with the Divisions of Maternal and Child Health

and Vital Statistics, for their assistance in furnishing data and personnel in the preparation of this report.

ROBERT O. BLOOD, M.D., *Chairman*
BENJAMIN P. BURPEE, M.D.
FREDERICK S. GRAY, M.D.

TABLE 1. *Maternal Deaths, by Cause (As Classified by the Committee).*

CAUSE	NO. OF DEATHS
Hemorrhage of childbirth and the puerperium — accompanied by complications of placenta	5
Toxemia of pregnancy	2
Puerperal pulmonary embolism	1
Total	8

TABLE 2. *Maternal Deaths by Groups According to Responsibility for Deaths.*

GROUP	NO. OF DEATHS
I	1
II	0
III	7
IV	0
Total	8

TABLE 3. *Maternal Death Rates per 1000 Live Births, 1933–1949.*

YEAR	RATE	YEAR	RATE
1933	6.3	1942	1.7
1934	5.4	1943	2.7
1935	6.1	1944	2.9
1936	4.8	1945	1.8
1937	4.3	1946	1.4
1938	3.8	1947	1.1
1939	3.1	1948	1.1
1940	3.1	1949	0.065
1941	1.9		

Number of births in 1949: 12,229.

TABLE 4. *Fetal Causes in Resident Stillbirths.*

CAUSE	MALES	FEMALES	SEX NOT DETERMINED	TOTAL
Difficulties in labor:				
Difficult labor with malposition of fetus	0	1	0	1
Placental and cord conditions: cord condition without mention of placental abnormality	16	19	0	35
Placenta praevia	2	2	0	4
Premature separation of normally implanted placenta	18	17	0	35
Placenta praevia with cord abnormality	0	1	0	1
Premature separation of normally implanted placenta with cord abnormality	1	0	0	1
Placental infarct	1	3	0	4
Other abnormality of placenta and cord	5	4	0	9
Birth injury:				
Birth injury with abnormality of bones of pelvis	2	0	0	2
Birth injury with abnormality of organs or tissues of pelvis	0	1	0	1
Birth injury with malposition of fetus	2	2	0	4
Birth injury with abnormality of forces of labor	1	0	0	1
Congenital malformation of fetus:				
Anencephalus	3	10	0	13
Hydrocephalus	4	2	0	6
Spina bifida	1	1	0	2
Other malformation of central nervous system	2	0	0	2
Monstrosity	3	2	2	7
Other and unspecified malformations	2	1	0	3
Diseases of fetus and ill defined causes:				
Erythroblastosis	5	5	0	10
Maceration, cause not specified	1	3	0	4
Other ill defined cause	17	7	0	24
Not stated	31	19	3	53
Totals	117	100	5	222

TABLE 5. *Maternal Causes in Resident Stillbirths.*

CAUSE	MALES	FEMALES	SEX NOT DETERMINED	TOTAL
Chronic diseases in mother:				
Diabetes mellitus	0	3		3
Chronic disease of genitourinary system	0	1		1
Acute diseases in mother:				
Pneumonia	0	1		1
Other acute disease or condition	1	1	1	3
Diseases and conditions of pregnancy and childbirth:				
Hemorrhage without mention of placental condition	0	1		1
Eclampsia	3	0		3
Other toxemias of pregnancy	9	3		12
Infection	1	0		1
Difficulties in labor:				
Difficult labor with disproportion but no mention of abnormality of pelvis	0	1		1
Difficult labor with malposition of fetus	3	2		5
Difficult labor with abnormality of forces of labor	1	0		1
Difficult labor with operative delivery	0	1		1
Difficult labor with abnormality of organs or tissues of pelvis	1	2		3
Other causes in mother:				
Fall	1	2		3
Overexertion	0	1		1
Other and ill defined causes in mother	2	1		3
Maternal cause not stated:	92	74	4	170
Ill defined cause	3	6		9
Totals	117	100	5	222

TABLE 6. *Resident Stillbirths.*

COUNTY	INFANTS BORN IN HOSPITAL	INFANTS BORN AT HOME	TOTAL
Belknap	9	1	10
Carroll	11	0	11
Cheshire	5	0	5
Coos	12	2	14
Grafton	24	3	27
Hillsborough	70	2	72
Merrimack	27	3	30
Rockingham	18	3	21
Strafford	17	2	19
Sullivan	12	1	13
Totals	205	17	222

TABLE 7. *Maternal Deaths by Cause and County of Occurrence.*

CAUSE	COOS	GRAFTON	HILLSBOROUGH	MERRIMACK	ROCKINGHAM	TOTAL
Toxemia of pregnancy	1				1	2
Hemorrhage of childbirth and puerperium accompanied by complication of placenta	1	1	2	1		5
Puerperal pulmonary embolism			1			1
Totals	2	1	3	1	1	8

Dr. Brown, on behalf of the Committee on Officers' Reports, endorsed Dr. Daily's letter, as printed in the report of the Committee on Maternal Health and Infant Welfare and emphasized the importance of continuing along the same lines. He moved that the report of the Committee on Maternal and Child Welfare be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The report of the Committee on Alcoholism was presented, as follows:

During the past decade there has been developing on a nationwide scale an encouraging trend on the part of the lay populace and the medical profession to regard alcoholism as a disease that can be treated and prevented. World War II, with its neuropsychiatric casualties both at home and abroad, did much to highlight the importance of psychosomatic medicine. It was only natural, then, that studies on alcoholism should go hand in hand with studies of personality disorders. The New Haven group has done much to spearhead the attack on this problem, and in 1943 the Yale Plan Experimental Clinic came into being, the State of Connecticut Commission on Alcoholism being organized in 1944. New Hampshire and Wisconsin almost simultaneously authorized the investigation of the problem in 1945, and in 1947 New Hampshire became one of the pioneer states to inaugurate a fully functioning commission on alcoholism.

The New Hampshire Medical Society, recognizing the importance of this work, appointed a committee on alcoholism to further the interest in this subject and to study the problem from the medical standpoint. This committee has worked with the Commission, and already various hospitals over the State are set up and are helping in the rehabilitation of the alcoholic.

With the recent introduction of Antabuse new interest has been aroused in the problem all over the world, and the alcoholic is now being offered the services of psychiatrists, internists, social workers, medical investigators and Alcoholics Anonymous working together as a team in the treatment and prevention of this disease.

In June of this year letters of invitation were sent to physicians throughout the State inviting them to a seminar on the Medical Care of Alcoholism held at the Millville Inn, Concord. Dr. Sidney Berman, psychiatrist-in-charge of the Connecticut Clinic on Alcoholism, gave a very enlightening and stimulating discussion of the problem from a medical-psychiatric standpoint, while Dr. Ruth Fox, director of the New York Treatment Center for Alcoholics, concentrated her remarks on her extensive work with Antabuse. The meeting was held on the evening of June 23 and was preceded by a dinner at the Millville Inn. It was believed by the majority who attended that Dr. Fox and Dr. Berman did much to stimulate interest in the subject and to help crystallize the thinking of those present regarding the alcoholic problem.

Plans are being made for an open meeting at the time of the New Hampshire Medical Society meeting at the Mount Washington House in September, and ways and means will be discussed for wider dissemination of knowledge to all the physicians in New Hampshire regarding the care and rehabilitation of the alcoholic.

The Committee on Alcoholism wishes to acknowledge the fine work being done by the New Hampshire State Commission.

JOHN H. BRANSON
JOHN MCKENNA
BERNARD ROBINSON

Dr. Brown moved that the report of the Committee on Alcoholism be included in the minutes of the meeting.

This motion was duly seconded and was carried.

The report of the Committee on Tuberculosis was then presented:

Your committee is happy to report that the year 1949 recorded a new all-time low in the tuberculosis mortality in New Hampshire. The year 1948 recorded 72 deaths from all forms of the disease and a death rate of 13.8 per 100,000 population for our state. The provisional figures for the year 1949 are 62 deaths (all forms) and a rate that is closely approaching 10 per 100,000 population. The tuberculosis mortality statistics for all states of the union are not available as yet. However, we have reason to believe that the New Hampshire death rate for 1949 will be among the six or seven lowest among the states of the nation.

In 1948 only one state in the country had a tuberculosis death rate lower than 10 per 100,000 population. In that year Iowa recorded a rate of 9.5 per 100,000 population. New Hampshire's low tuberculosis mortality rate is particularly gratifying in view of the fact that it is one of the most highly industrialized states in the nation in proportion to its population, in the second or third place in this classification. It is recognized that there are, in all probability, a number of reasons for the decline in the morbidity and mortality from tuberculosis during the past forty-three years. It is difficult to evaluate the relative influence of favorable economic and social conditions for the masses of people, and of activities in the nationwide campaign for the prevention and cure of the disease in bringing about this favorable result. Nevertheless, during the past forty-three years the nation has been subjected to conditions that usually tend to increase the mortality and morbidity from tuberculosis — namely, wars and economic depressions. Wars increase hours of labor and nerve tensions, and economic depressions lower nutrition. Yet despite these adverse conditions in the nation since 1917, the tuberculosis death rate has continued to decline, and the rate of decline has been definitely accelerated during the past twelve years.

During the past forty-three years the campaign for the prevention and cure of tuberculosis has grown to great proportions throughout the nation. During this period we have witnessed a demonstration of the practical idealism of the American people in their spontaneous support of and wholehearted participation in the entire campaign of prevention and cure of tuberculosis. Hundreds of sanatoriums have been built by states, counties, cities and the federal Government, providing approximately 90,000 beds for the treatment and segregation of tuberculosis patients. Facilities for the early detection of persons harboring tuberculosis have been tremendously increased particularly through the use of the chest x-ray examinations in hospitals, in physicians' offices, in chest diagnostic clinics, and of late years, through traveling x-ray mobile units, which are equipped to examine rapidly large numbers of workers in industry and even entire populations in communities.

Furthermore, our resources for treatment and control of the disease have been tremendously augmented through chest surgery and the use of antibiotics. Thousands of tuberculosis patients, formerly considered hopeless cases, have been saved by chest surgery, the skillful use of antibiotics and improvements in sanatorium treatment. Even though the various services for the control of the disease comprise only one of several factors, there is good reason to believe that they form the decisive factor. It is self-evident that services that reduce the reservoir of tubercle bacilli among human beings in any community will lessen the number of new cases of tuberculosis. Every active case of tuberculosis or potentially infectious case discovered and brought under treatment and supervision is a step forward in reducing this reservoir of human tubercle bacilli. In the aggregate these measures represent the weight that is bringing about the control of this disease in our state and nation.

It has been demonstrated that a large number of cases, even of active pulmonary tuberculosis, have no symptom or symptoms so slight as to escape notice. This is the justification for the mass survey method for tuberculosis detection, which has advanced in the United States to the point where at present approximately 14,000,000 people annually undergo chest x-ray examinations. It is important that mass survey programs be enlarged, but at the same time all other methods that promise disclosure of a considerable number of tuberculosis cases must be utilized.

In particular, we emphasize that 60,000,000 to 80,000,000 Americans, for one reason or another, annually consult physicians, and it has been demonstrated that the tuberculosis rate among these groups is higher than among the general population. For this reason, it is highly desirable that private physicians, including general practitioners, internists and specialists, obtain a chest x-ray film of every patient who consults them unless the results of a recent chest x-ray survey are available. Your committee has good

reason to believe that the low tuberculosis mortality and morbidity rate in our state is due in considerable part to the fact that the physicians of New Hampshire have availed themselves for many years of resources for chest x-ray examination for all their patients who might be classified as suspicious cases. These resources include the offices of radiologists and internists, the hospitals, and the chest diagnostic clinics held in all sections of the state under the auspices of the New Hampshire Tuberculosis Association and health departments.

Your committee again urges increasing the use of chest x-ray examinations and utilization of all resources through which chest x-ray studies may be made available. In this connection your committee urges that the members of our society arrange for prompt follow-up study upon all cases referred to them through the mobile unit mass chest x-ray services of the New Hampshire State Department of Health. This mobile unit provides rapid mass chest x-ray services, which have already secured x-ray examinations for a large part of our population. The mobile unit 70-mm. films must be followed up by the standard 14 by 17 films and further examinations for final decisions about the chest lesion, which may be inactive or active pulmonary tuberculosis, old pleuritic adhesions, new growth of the lungs, bronchiectasis, lung abscess, abnormalities of the heart and so forth. A great many of these referrals from the mobile unit concern persons representing few, if any, symptoms. This is particularly true with reference to individuals whose films present findings consistent with a diagnosis of pulmonary tuberculosis. It is true that a great many of these patients will ultimately be proved to have a stabilized or spontaneously healed pulmonary tuberculosis.

However, they are potential cases of active disease requiring preventive treatment and supervision. Furthermore, every effort should be made to prove that the pulmonary tuberculosis is inactive. This is, in many cases, an exceedingly difficult task. Absence of symptoms, the appearance of good health and unwillingness for more examinations require patience on the part of the physician and the patient. Often a series of chest x-ray films is required to prove stability or instability of the lesion visible on the microfilm.

It is probable that the time is approaching when screening of the general population for tuberculosis may be combined and co-ordinated with other screening programs for other important pathologic conditions, such as cardiovascular disease, cancer, syphilis and diabetes — similarly characterized by relatively long subclinical periods in which detection may be life saving or important to community protection.

Approximately five years have elapsed since the announcement of certain antibiotics as possible favorable factors in the treatment of tuberculosis. Much has been learned about the value and limitations of these drugs. This report will not endeavor to cover all these points. Considerable literature is available on the types of cases in which these antibiotics appear to be of the most value. The studies up to this time seem to indicate that streptomycin is the most promising drug in tuberculosis treatment. Its use is particularly to be combined with sanatorium treatment and chest surgery.

A handicap in the use of streptomycin has proved to be the tendency of certain strains of tuberculosis germs to become resistant to the action of the drug. Col. Carl W. Temple, Medical Corps, United States Army, at a recent meeting of the National Tuberculosis Association held in Washington, D. C., declared that the most satisfactory results in preventing or delaying the emergence of resistant strains of tubercle bacilli were obtained at the Army Medical Center when streptomycin was used in combination with para-aminosalicylic acid (PAS) on an intermittent regimen — that is, streptomycin was given every three days and PAS every day for a period of four months. This is the procedure now carried out at the sanatoriums at Glencliff and Pembroke.

Through the interest of the president of the New Hampshire Medical Society, Dr. John P. Bowler, Governor Sherman Adams, the State Health Department, the trustees of the New Hampshire State Sanatorium and others active in the campaign against tuberculosis, the recent special session of the New Hampshire Legislature provided for a state tuberculosis commission to be appointed some time after July 1, 1950. The Commission will undoubtedly bring about a closer co-ordination of the various official and voluntary agencies engaged in the field of tuberculosis control throughout the state.

The Commission will also clarify policy and procedure for admission of patients to the New Hampshire State Sanatorium at Glencliff and the private sanatorium at Pembroke, which for many years has devoted its entire resources to the treatment and care of tuberculous patients as state beneficiaries under the appropriation for sanatorium treatment for advanced cases in institutions approved by the State Department of Health and the State Department of Public Welfare.

ROBERT B. KERR
FRANK G. SELDON
JOHN D. SPRING

Dr. Brown moved that the report of the Committee on Tuberculosis be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The following report of the Committee on Medical Economics was presented:

Under the existing national conditions, a great many of the problems of medical economics are being handled at present by the Executive Committee of the Society. Therefore, the report of the Committee on Medical Economics will be restricted to the Blue Shield program.

On the operational level, the experience during the past year has continued to register a high loss ratio on the surgical service, although somewhat lower than during the preceding year. The continuation of this high loss factor was sufficient to pull the reserve funds down below a sound level, and, for this reason, the Board of Directors reluctantly voted at a meeting held in May of this year to authorize an increase in the rates for the surgical service, to take effect July 1, 1950. Blue Cross also was compelled to increase its rates concurrently, and the effect of these increases on enrollment remains to be seen.

The proposal for a service contract under the surgical division received considerable discussion during the year on a county and committee level. A number of questions have been raised regarding this proposal, and consideration of the problem is being continued. The development of a service contract would unquestionably be a factor of great importance in our public relations.

On the organizational level, two significant developments have occurred during the past year. Liaison committees have been organized in the staffs of most of the hospitals in the two states, and these have been of great value in providing mutual understanding and mutual solutions of the various problems connected with Blue Shield operations. More recently, in order to give the members of our societies a more direct voice in the conduct of Blue Shield affairs, two state advisory committees have been set up. The Vermont committee consists of the Council, which comprises representatives from each component society. The New Hampshire committee consists of one member from each county society, for the present appointed temporarily by the president of each county society, but in the future to be elected by each county society. It is proposed that these advisory committees shall make nominations for members of the Board of Directors and in general shall advise the Blue Shield Board on all matters pertaining to professional relations. At present, these committees are engaged in a reconsideration of the schedule of benefits.

On the national level, the Blue Shield National Insurance Agency has been incorporated, and the necessary capital stock is now being raised by subscription among the member plans. The necessary total has now almost been reached, and it is anticipated that the actual establishment of the national company will proceed to completion in the near future.

Your committee recommends the continued support of the Blue Shield program on the part of all members of the New Hampshire Medical Society.

LESLIE K. SYCAMORE
FRANCIS J. DUBE
JOSEPH N. FRIBORG

Dr. Brown then moved that the proposal in the report of the Committee on Medical Economics regarding State Blue Shield representation be referred to the Executive Committee, to be considered in connection with the total committee revision previously agreed to.

This motion was duly seconded and was carried.

Dr. Brown, for the Committee on Officers' Reports, moved that the report of the Committee on Medical Economics be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

Dr. Theobald then read the report of the Committee on Allied Professional Relationships.

On Sunday, August 6, 1950, at the Wentworth Hotel, a meeting was held at which Dr. Louis C. Theobald and Dr. Loren Richards represented the New Hampshire Medical Society, and Mr. John H. Greenaway, Mr. Alton Tobey and Mr. Clarence Hounsell, with Dr. George A. Moulton, represented the New Hampshire Pharmaceutical Association. This was the first meeting of the Committee on Allied Professional Relationships with the committee from the New Hampshire Pharmaceutical Association on Inter-Professional Relations of which Mr. Greenaway is the chairman. Dr. Ralph W. Tuttle, of Wolfeboro, was unable to be present. The meeting was carried out with an unusual and extremely satisfactory degree of harmony, and we physicians were impressed by the thoughts that came from the discussion and by the orderly and mannerly way in which Mr. Greenaway carried on the meeting.

This Inter-Allied Committee relationship is the result of several years of thought by Dr. Moulton, who is the executive secretary of the Pharmaceutical Association, and is the answer to the problem presented by Dr. Bowler at the last meeting of the House of Delegates. It is also the result of considerable pressure brought by the New Hampshire Pharmaceutical Association and the national pharmaceutical organization to clarify the situation that has been broadly called the "dispensing by physicians." However, the meeting went farther than that, for it clarified many points that might be considered as complaints by the physicians and by the pharmacists themselves.

Mr. Greenaway prefaced the discussion by giving a detailed and interesting account of the training of a pharmacist, attempting to show that the standards and integrity of pharmaceutical practice are on a par with those of any other profession. He discussed briefly the requirements a student needs to have and to maintain in order that he might meet the necessary standards for admission and graduation from a school of pharmacy. He showed that these have become increasingly more strict so that the student can graduate and stand on a par with other professional men. We think that this point is well taken because nowadays the pharmacist is no longer an apprentice, as in medicine, in which the apprenticeship of the physician is no longer an accepted way of training. Comments were then made about the requirements for the opening of a store by a pharmacist, inasmuch as they must meet a minimum requirement of stock and equipment, as well as the legal requirements and limits. It is not possible for anyone to open a store and include a pharmaceutical inventory in it, for it must first be acceptable to the examining board of the pharmacists.

Mr. Greenaway then went on to discuss the contribution of the pharmacists to the campaign that the American Medical Association is carrying out to prevent a socialized medical program. The pharmaceutical associations have distributed considerable literature aimed directly at socialized medicine and its various programs and have disseminated information on public health and preventive medicine. The pharmacists have distributed literature on cancer, syphilis, tuberculosis and other phases of public health, which has been an important and conscientious aid toward the elevation of the standards of health in this country. This, we think, is a factor that we fail to appreciate because it is a publicity campaign directly from the pharmacist, and not necessarily directly from the medical profession through the medium of the pharmacist. Therefore, we believe they should get credit where credit is due.

Prescription blanks were then discussed. Doctors presented the viewpoint that it probably was not good practice for the druggist to use the prescription blank as a direct or indirect means of advertising. The pharmacists accepted this viewpoint. This is probably a custom handed down from many years of service, and it is a service to the physician, inasmuch as a very great majority of the physicians use prescription blanks furnished by the pharmacists. This eliminates the cost and bother of private printing of the blanks.

However, it seems probable that the pharmacists are knowingly or unknowingly causing a certain degree of direct advertising, and also a lack of freedom of choice of drugstore by having the prescription blank carry the stamp of the pharmacist who prints the blank It was decided that perhaps it would be well worth while to suggest to the pharmaceutical group that they discontinue the printing of prescription blanks carrying a name or stated drugstore on the face or on the reverse. It was also decided that perhaps the prescription blanks could be arranged or printed in such a fashion that the legend would be more specific, and a sample blank was brought in that had a printed legend stating that the prescription could be filled once, twice, as necessary, or not at all, and likewise, that a prescription itself might be copied — yes or no. This would carry out a degree of uniformity and would make it unnecessary for the patient to return to the doctor for further prescriptions, or would make it a necessary provision if the drug prescribed required a second prescription.

There was some discussion of the distribution of samples by physicians. Apparently, in many cases, especially when a drug is labeled by its manufacturer "not to be distributed unless by the prescription of a physician," it is unwise and perhaps illegal to distribute samples to patients. It creates considerable difficulty to the pharmacist when a patient brings in a sample tube or pill box and asks the pharmacist to refill it. This is impossible when the sample carries on its label the notation that it cannot be filled without the prescription of a physician.

Another point of discussion that it might be well for physicians to consider, because it has a great interest to the pharmacist, is the state distribution of drugs and serums. This problem probably goes beyond the realm of control of either the physician or the pharmacist because it is a national public-health program. However, many of our serums are now distributed to the State by federal funds. Originally this program started as a means of relieving the cost of "expensive medications," but it is now rapidly covering many more of the vaccines and serums that certainly are not in the expensive group. It is possible for any physician to get many of these things by simply applying at the city hall, and therefore it takes away a source of income from the pharmacists. It is something that the combined efforts of the two societies can well make a study of.

Prescription over the counter direct to people, escaping the channel of the doctor, was then discussed. This is probably the fault of the patients and not necessarily of the doctor or the pharmacist. We believe that the physician has a legitimate complaint, but, on the other hand, if a person calls in a drugstore and wants a cough syrup or headache pill or poison-ivy treatment, this does not necessarily seem to the druggist as being an evasive measure or direct prescription over the counter. The pharmacists believed that one contribution by which they can improve our relations, will be to carry out an educational program throughout their society in an attempt to cut down as much as possible any so-called over-the-counter prescription.

The advertising methods of the drugstores were then considered. Certain "boiler-plate" advertising is out of the control of the pharmacists. Such advertising is not conducive to good pharmaceutical practices, but on the other hand it is beyond the control of the local drugstore. Advertising as it is carried on by certain drugstores with

a national affiliation is not acceptable, and that is a problem that the pharmacists must settle among themselves.

The great problem is the physician-owned or physician-group-owned pharmacies, which do not allow the free choice of pharmacist. This, of course, is important because it hits back at our theme — namely, the free choice of the physician — and should therefore receive some serious consideration. The pharmacists have apparently made a serious approach to the American Medical Association about this, and the Association has answered by including, in its *Principles of Medical Ethics*, a paragraph regarding the dispensing of drugs. Section 6, as printed in the pamphlet, *Principles of Medical Ethics of the American Medical Association states*:

> An ethical physician will not receive remuneration from patients on the sale of surgical instruments, appliances and medicines, nor profit from a copyright on methods or procedures. The receipt of remuneration from patents or copyrights tempts the owners thereof to retard or inhibit research, or to restrict the benefits derivable therefrom to patients, the public, or the medical profession. The acceptance of rebates on prescriptions or appliances, or of commissions from attendants who aid in the care of patients is unethical. An ethical physician does not engage in barter or trade in the appliances, devices or remedies prescribed for patients, but limits the sources of his professional income to professional services rendered the patient. He should receive his remuneration for professional services rendered only in the amount of his fee specifically announced to his patient at the time the service is rendered or in the form of a subsequent statement, and he should not accept additional compensation secretly or openly, directly or indirectly, from any other source. The prescription or dispensing by a physician of secret medicines or other secret remedial agents, of which he does not know the composition, or the manufacture or promotion of their use is unethical.

The pharmacists readily accept the fact that physicians located in certain parts of the State where the drugstore is inaccessible must carry and must dispense certain drugs and other medicines that can be obtained by prescription in other sections. This is something that the physicians cannot control because of its necessity. Although it is probably true that physicians carry more drugs than is necessary, and dispense from their drug room certain things that could be prescribed, we believe that the physicians must make a determined effort to bring this situation within the realm of ethics. Of course, it is true that a man in this country, where democracy is the way of life, may choose his way of livelihood, and if he chooses to be owner or part owner of a drug house, *except for the ethics involved*, there is no legal way in which he may be forced to discontinue the practice. The problem of physician-group-owned pharmacies in which there is a registered pharmacist is one for discussion at a later time by the House of Delegates.

In conclusion, it may be stated that the meeting was really a success. The druggists have a program that is fitting and worthy of discussion. We believe that the Committee on Allied Professional Relationships should be continued as a means of contact not only with the druggists but also with the other professions, such as dentistry and nursing, and as a means of actual co-operation with their committees. We believe that the Committee should be requested to meet at least once or twice a year and present a report annually to the House of Delegates. The New Hampshire Pharmaceutical Association will stand behind the program to keep medicine a profession of individualism and to work to prevent its nationalization. With the proper co-operation, I am sure that their contribution will be worth while.

Dr. Brown pointed out that when the Committee on Officers' Reports moved to record a report in the minutes, it did not dispose of the question, which was still open for discussion. For the Committee on Officers' Reports he moved that the report of the Committee on Allied Professional Relationships be referred to the Executive Committee, or the Committee on Constitution and By-Laws, because this was a special committee reporting to the officers.

This motion was duly seconded and was carried.

Dr. Brown, for the Committee on Officers' Reports, then moved that the report of the Committee on Allied Professional Relationships be included in the minutes of the meeting.

This motion was duly seconded and was carried.

The report of the Committee on Public Health was then presented, as follows:

> The reorganization of the State Health Department has been the principal concern of the Committee for the past year. The consolidation of the various health agencies under the Department has been needed for a long time, and although the final setup does not include all agencies it is a great improvement over the old.
>
> It will now be possible for one inspector to make all types of inspection in a town pertaining to sanitation, barber shops, factories, stores, shops, beauty parlors, check weights and measures, make sanitary surveys, answer complaints relative to above and carry out a well rounded public-health program.
>
> This arrangement would fit in very well with the proposed county health unit organization as set forth in this committee's last year's report.
>
> Much time was spent in discussion of the reorganization, which goes into effect July 1, and it would seem that it was of some material benefit to the legislators.
>
> DONALD G. BARTON
> HARRY W. SAVAGE

Dr. Brown moved that the report of the Committee on Public Health be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The following report of the Committee on Public Relations was then presented:

> For more than a year this society has been involved necessarily, but not entirely by its own choice, in many and varying phases of public relations. Most have been a part of a planned and organized effort of our own direction. Others were thrust upon us. All, however, focused a certain amount of attention, from the viewpoint of the lay public, not only upon the Society as a whole but upon specific members of the profession.
>
> Our report will deal only with what the Society has attempted to do in the field of public relations, what it has accomplished in applied public relations and what course might well be pursued in the forseeable future.
>
> Our public-relations goals are not necessarily new. Some have merely been re-emphasized during this period of nation-wide activity brought about through the controversy over nationalized health, which has made it apparent that organization will remain vital so long as this issue persists.
>
> Many doctors have been applying public-relations principles in their every-day activity and association with one another and with the lay public. Directing this individual effort into organized channels on a state-wide basis in order to inform the general public more adequately has been the objective of our effort.
>
> This society's efforts during the year have been directed toward the formulation and implementation of six basic points falling under the province of the public-relations committee. These points are reviewed briefly merely for the purpose of segregation and identification. They are as follows: to meet community needs as to the adequacy of night and emergency call systems; to establish some central review committee called for the lack of a better name, a state grievance committee; to encourage all phy-

sicians to exercise leadership in solving community health problems; to encourage doctors to participate more fully in local health campaigns such as diabetes detection and chest survey programs; to encourage patients to provide for themselves prepaid medical care to a degree that those requiring medical care will not hesitate to seek it; and to develop better relations with the press and radio.

With a further view toward extending our public relations, meetings have been held with representatives of the New Hampshire Association of Accident and Health Underwriters for a discussion of mutual problems. Similar personal contacts have been made with other allied professional groups including the New Hampshire Dental Society and the New Hampshire Hospital Association. Development of a new state-wide Blue Shield Committee with membership representation from all County Medical Societies will strengthen our relationships with each other and with lay groups in general.

To be presented members of the House of Delegates at the annual meeting will be a "code of co-operation" drawn up by editors and publishers of weekly and daily newspapers and by those associated with the radio industry. This code is another step in the field of applied public-relations by which our aims and objectives could be co-ordinated with those of the statewide information mediums with resulting benefit to all concerned.

This "code of co-operation," which may be further amplified by the Society's public-relations committee, appears below for the information of the members:

1. The executive officers of the New Hampshire State Medical Society shall be available at all times to the representatives of the press and radio in order that authentic information may be obtained as promptly as possible on health and medical subjects. If the information is not immediately available, it shall be the function of the executive office, or such individual or representative of the Society as the Executive Committee may direct, to obtain the information desired or locate a competent authority from whom the press or radio may obtain it directly.

2. Officers, committee chairmen or designated spokesmen of the New Hampshire State Medical Society may be quoted by name in matters of public interest for the purpose of authenticating information given. This shall not be considered by their colleagues as a breach of traditional practice of physicians to avoid personal publicity, since it is done in the best interests of the public and the profession. County medical societies are urged to adopt a similar policy with respect to their officers, committee chairmen, and designated spokesmen.

3. Hospital authorities should recognize that time is an all important factor in newspaper work. It would seem wise, therefore, that each hospital have someone available at all times to deal with representatives of the press and radio and that the name of this hospital representative or his delegated authority in his absence, be available to information and/or switchboard operators, so that inquiries from newspapers may be expedited. Persons delegated to talk with the press and radio should be familiar with the fundamental principles of the code governing relations between the hospitals and the press and radio and within the limits of such code co-operate with the newspapers and radio.

4. The foregoing are general principles designed to contribute to a better working relationship between the medical profession and the press and radio. The following rules have been developed as a guide in specific instances and are fundamental.

(a) Attending Physician

Hospitals should give the name of the attending physician to the newspaper, when so requested. The newspaper shall not use the physician's name without his consent.

(b) Private Cases

The presence of certain patients in a hospital in whom the public has a rightful interest, is news. Their presence should generally be acknowledged by the hospital unless expressly forbidden by the patient or attending physician.

(c) Emergency Cases

Certain items of public interest are a matter of police or fire department record, and are available from these records.

For such cases, the hospitals should promptly give the following information:

Name, age, sex, marital status, address, occupation, and employer.

Nature of the accident — such as automobile, explosion, shooting, etc.

Extent of injuries — such as fractures, burns, wounds, etc., and to what part of the body. It is understood that pending complete prognosis, these statements may of necessity have to be hedged with "possible fractures," "condition apparently good, fair or serious," etc.

(d) When newspapers request the privilege of photographing a patient in the hospital, such permission will only be given (A) if the patient gives consent and if in the opinion of the doctor in charge of the case, the patient's condition will not be jeopardized, and (B) if the patient is a minor, the parents or guardian are willing to have a photograph taken.

(e) Deaths

The death of any patient is presumed to be a matter of public record. A statement that the patient has died should be made by the hospital. This is vital in areas where local hospitals serve a large adjoining area.

(f) Births are a matter of public record and hospitals should assume the obligation to give full information concerning the same, without the right of self censorship, including facts such as parents' names, mother's maiden name, parents' address, time of birth, etc. These should be the minimum standards. Physicians and hospitals should keep in mind a news story can be no more accurate than the source of information.

Most of the details connected with the furtherance and implementation of the program placed in operation by your committee have been left to public-relations counsel as to administration. This has been largely true in respect to liaison work, which is an intricate part of any organization's public-relations policy. The success of this effort is not difficult to measure when it is realized that the medical profession in New Hampshire now enjoys reasonably good public relations, and that these did not develop spontaneously.

We believe the adoption by the Society of something along the lines of the "code of co-operation" together with a not too flamboyant public-relations program, as well as the continuation of the 1950 program and further development of the above mentioned six points, will provide the Society in 1951 with something constructive and beneficial.

JOHN P. BOWLER
DEERING G. SMITH
FRANCIS BROWN
LLOYD L. WELLS

Dr. Brown then stated the Committee on Officers' Reports noted that the report of the Committee on Public Relations was mainly concerned with either a record of what it had done or with recommendations that would be taken up, specifically, under the matter of a grievance committee, in the report of the Committee on Amendments to the Constitution and By-Laws.

The one specific recommendation that the delegates were called upon to vote on was the code of co-operation, as stated in this report. The Committee on Officers' Reports, after consideration, had decided to make some recommendations, the first of which was to strike out the parenthetical headings

such as "(Items 1 and 2 based in part on the Colorado code)." Secondly, the code might be redrafted to exclude explanatory remarks in what is numbered "3": "It would seem wise, therefore, that each hospital have someone available . . ." The Committee on Officers' Reports questioned whether this was necessary in a code of co-operation.

Then in Paragraph 4 (e), the last sentence was unnecessary: "This is vital in areas where local hospitals serve a large adjoining area."

The most important change was in the following statement in Paragraph (f):

> (f) Births are a matter of public record and hospitals should assume the obligation to give full information concerning the same, without the right of self-censorship, including facts such as parents' names, mother's maiden name, parents' address, time of birth, etc.

The Committee on Officers' Reports recommended the addition of the sentences "Provided the mother consents to the publication of the birth." The Committee also suggested that the last two sentences be stricken out.

Dr. Brown moved that the code, Paragraph 4 (f), be amended by the addition of the statement: "Provided the mother consents to the publication of the birth," at the end of the first sentence, and that the last two sentences be deleted in 4 (f).

President Bowler pointed out that the New Hampshire Hospital Association had asked that the phrase "without the right of self-censorship" be deleted.

Dr. Brown retracted his amendment and moved that the phrase "without the right of self-censorship" be stricken out.

This motion was duly seconded and was carried.

Dr. Brown moved that the code be referred back to the Committee on Public Relations.

This motion was duly seconded and was carried.

Dr. Brown, for the Committee on Officers' Reports, next moved that the report of the Committee on Public Relations be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The report of the Committee on the Control of Cancer was then presented, as follows:

> During the past year a change was made in the medical education program. Instead of the usual informative letters, your committee, through the very generous co-operation of the Field Army of the American Cancer Society, decided to have mailed to each member four pamphlets published by the American Cancer Society. For various reasons, the publication of these pamphlets has been delayed, and only two have been sent to our members. These pamphlets are valuable and easily readable. The titles are: *The Diagnosis of Genito-Urinary Tumors, The Value of Early Diagnosis in Malignant Lymphomas and Leukemia, The Early Diagnosis of Breast Cancer, Cancer of the Lung.* We expect the remaining pamphlets to be issued and sent in the near future.
>
> Also sent to each member of the Society was the very concise and well written second edition of the *Cancer Manual* published by the Massachusetts Division of the American Cancer Society, Inc. This manual covers briefly recent information regarding practically all types of cancer, and should be used as a desk reference. The New Hampshire Medical Society is deeply indebted to the Field Army for the financial contribution making it possible for all members of the Society to own the pamphlets and the *Cancer Manual.*
>
> The annual cancer conference conducted by your committee and also financed by the Field Army, was held on April 18, 1950, and the papers were interesting, instructive and productive of discussion. As these conferences are intended for the information of the general practitioner as well as those more particularly interested in cancer and its treatment, it is unfortunate that so few general practitioners attend.
>
> The sincere and apparently tireless group of women active in the Field Army deserve much credit and also deserve our active interest and participation in their work. All physicians should realize what they have accomplished in fourteen years. In part, their activities consist of distribution of thousands of pieces of literature for lay education, distribution of posters, making surgical dressings for indigent cancer patients, transportation of patients to hospitals and clinics, education in high schools, support of a fellowship in cancer pathology at Dartmouth, and aid to medical education described above.
>
> Early in 1950, at a meeting of physicians and lay people, there was created the New Hampshire Cancer Society, Inc., a division of the American Cancer Society, Inc. Membership in this organization may be had by the payment of $1 dues. The Field Army will continue its program as an integral part of the cancer society.
>
> The state cancer clinics have increased in attendance, and for the third time, the Cancer Comission has been obliged to ask for more money on account of more cancer patients needing assistance and because of the gradually rising hospital costs.
>
> As the purchasing and distribution costs of the cancer pamphlets and the *Cancer Manual* were assumed by the Field Army, your committee has expended only $33.75 of the $70 appropriated for our use. As our plans for next year are not completed, we request an appropriation of $75.
>
> GEORGE C. WILKINS
> GEORGE F. DWINELL
> RALPH E. MILLER
> WALTER H. LACEY
> JOHN R. PERLEY
> JAMES W. JAMESON

Dr. Brown then stated that the Committee on Officers' Reports recommended deferring the consideration for request of appropriation until a consideration of the whole budget was taken up, and he moved that the report of the Committee on the Control of Cancer be recorded in the minutes of the meeting.

This motion was duly seconded and was carried.

The following report of the Committee on Emergency Medical Service was presented:

> Since the last report submitted by this committee in May, 1949, the State of New Hampshire has enacted a civil defense act. This is titled Chapter 304 of the Public Acts and Joint Resolutions of the Legislature of 1949, an Act Relating to the Establishment of the Civil Defense Agency and Providing for Military Defense at Interstate Bridges and so forth. This law creates a division of civil defense, a state director of civil defense and a civil defense advisory council. The director, appointed by the Governor with the advice and consent of the Council, is responsible to the Governor for carrying out the program for civil defense of the State, co-ordinating the activities of all organizations for civil defense within the State, both state and local, and maintaining liaison with and co-operating with civil defense agencies and organizations of other states and the federal Government, and executing such other authority, duties and responsibility as authorized by the law or prescribed by the Governor. The Governor is authorized to prepare a comprehensive plan and program for the civil defense of the State, which is to be integrated into and co-ordinated with civil defense

plans of the federal Government and of other states; to co-ordinate the preparation of plans and programs of the political subdivisions of the State; to procure supplies and equipment; to initiate training and public information programs; to take all other steps necessary, including partial or full mobilization of civil defense organizations in advance of actual disaster; to make surveys of industries, resources, and facilities to determine capabilities for civil defense; and to plan for the most efficient emergency uses thereof. The act authorizes mobile reserve battalions and mutual aid agreements with other states and between the political subdivisions of the State. All civil defense personnel are required to sign a loyalty oath, and all political activity on the part of civil defense organizations is prohibited.

In accordance with the provisions of the act, the Governor and Council have appointed Admiral Miles Browning, of Warner, Director of Civil Defense. There is established under the law creating the Civil Defense Agency a civil defense advisory council consisting of the following members who shall serve *ex-officio*: the Governor, the president of the Senate, the speaker of the House of Representatives, the Attorney General and the State Director of Civil Defense, who shall constitute an executive committee of the council; one member each representing labor, industry, agriculture; and one member at large from each county, who shall be appointed by the Governor with the advice and consent of the Executive Council. This committee wishes to point out to the New Hampshire Medical Society that there is no provision under the law for representation of organized medicine on the Civil Defense Advisory Council. It is felt that this is a serious omission, and it is believed that a member representing the Society should be on this Civil Defense Advisory Council. The chairman of your committee in a conference with Admiral Browning called his attention to the fact that there was no provision under the law for having a medical representative on this council, and the director graciously agreed that this was an unfortunate omission, and he further stated that he would be glad to have a representative of the New Hampshire Medical Society on this council if this could be legally brought about by amendment of the law.

There is an excellent article by Charles W. Steele, M.D., Ralph A. Getchell, M.D., and Harry Butler, M.D., the members of the committee on Emergency Civilian Defense of the Maine Medical Association, which is published in the *Journal of the Maine Medical Association*, Volume 41, No. 3, March, 1950, entitled, "What Every Maine Doctor Should Know About Civil Defense and Public Safety Planning." Here the duties of the members of the Maine Medical Association are clearly outlined and there is given also a concise and clear outline of the use to which the medical and hospital facilities of the State of Maine should be put in case of disaster. This committee is indebted to these authors for a great many of the suggestions and recommendations that follow. These recommendations will have to do with the manner of providing the medical personnel that will be required for emergency hospital units in the general hospitals already in operation within the State, and for emergency hospital field units to operate auxiliary hospitals, to provide additional personnel for professional clearing station teams to operate emergency clearing stations and for professional first-aid teams to operate the emergency first-aid stations that would be required in the event of a disaster within the State. It is recommended that general hospitals be requested to cooperate with the New Hampshire Medical Society in an effort to work out a plan to provide emergency medical care for the civilian casualties in the State, and that they be asked to set up a procedure to operate in case of disaster locally, or to assist other areas when needed. They should also be requested to plan for maximum expansion of present bed capacities, to select alternate hospital sites, to train additional personnel and to develop plans for evacuating occupied beds.

Organization of active staff members of general hospitals for emergency duty should fall into a few categories such as professional medical personnel for duty at scene of disaster, personnel for emergency hospital units, personnel for surgical-medical auxiliary hospital field teams, and for professional clearing station field teams and first-aid teams.

A blue print of how the above recommended steps may be taken is appended herewith and made a part of this report, entitled Appendix A. It is copied from the recommendations made by the Maine Medical Association Committee on Emergency Civilian Medical Defense referred to above.

The Atomic Energy Commission and the National Security Resources Board have sponsored a group of courses entitled, "Medical Aspects of Atomic Warfare." Two physicians from New Hampshire attended this course in Rochester, New York. They were Edward W. Colby, M.D., Ph.D., of the New Hampshire State Health Department, and Frank Corbin Moister, M.D., of Dartmouth Medical School. Of these two men, we have lost one man by transfer, Dr. Colby having taken a position out of the State. The object of this course was to give intensive, comprehensive instruction in the medical aspects of atomic warfare, and to have the graduates of this course disseminate the instruction and knowledge they received to their fellow physicians within their own states. This course, which was of one week's duration, was also designed to help prepare the enrollees to serve as advisers in this phase of civil defense planning within their states. A basic training in radiologic defense was given to persons nominated by the governors of the various states, in courses of five weeks' duration, in certain installations of the Atomic Energy Commission. These courses were intended for the training of technical personnel other than physicians in the technic of monitoring and in the practical problems of radiologic defense. This course was of five weeks' duration, and it was intended that those attending these courses might be qualified to serve as monitors; that they might serve within their communities as instructors in related programs of instruction for technical personnel that might be required for radiological defense; and to help prepare them to serve as advisors in this phase of civil defense planning. The man who attended that course from this state was George Morrow, a State Health Department engineer.

The provision of large quantities of whole blood in case of a major disaster, especially of an atomic nature, in this state would constitute a real problem. There are few blood banks in actual operation in the State. There is a need for the activation of many more blood banks than now actually exist. There is a necessity in this state for an efficient system for blood procurement; expanded facilities for the matching and transfusion of blood; for the collection of blood, and facilities for reserve stores of bottles and donor and recipient sets. A committee is now engaged in ironing out the difficulties encountered along these lines. We believe that the Blood Bank Committee should be extended every aid possible in order to help them to accomplish their assigned tasks.

In conclusion, this committee wishes to make the following recommendations to the House of Delegates of the New Hampshire Medical Society: that the New Hampshire Medical Society seek active representation on the Civil Defense Advisory Council of the Governor; that the secretaries of the component county societies be requested to invite Dr. Frank Corbin Moister to speak at their county society meetings on the subject, "Medical Aspects of Atomic Warfare"; and that, if the House of Delegates approves the organizational procedure outlined in Appendix A of this report, it give authority to this committee to seek the active support of the component county-society committees on national emergency medical service in the institution of this program.

DANIEL J. SULLIVAN
CLARENCE E. DUNBAR
JOSEPH M. MCCARTHY
JOHN C. ECKELS
BERNARD J. MANNING

APPENDIX A

Recommendations are made by the Committee on Emergency Medical Service of the New Hampshire Medical Society:

1. General Hospitals to be Requested to:

a. Co-operate with the New Hampshire Medical Society in an effort to work out a plan to provide emergency medical care for civilian disaster casualties within this state.

b. Set up a standard operational procedure (SOP) with the least possible delay, which SOP would provide a detailed outline of procedure to be carried out in case of a disaster in their locality or to assist other areas when needed.

c. Prepare:

1. Plans for maximal expansion of present bed capacities.
2. Select alternate hospital sites if transfer becomes imperative.
3. Train additional personnel such as: laboratory technicians, surgical assistants, practical nurses and anesthetists.
4. Develop plans for evacuating occupied beds if disaster strikes.

2. Organization of Active Staff Members of General Hospitals for Emergency Duty.

a. The members of the active professional staff of each general hospital (with a bed capacity for 25 or more persons) be organized in a manner that will permit the following important functions to be carried out within the hospital by its active staff members in event of a local disaster.

1. Professional Medical Personnel for Duty at Scene of Disaster. Designate one or more experienced members of the medical profession in each larger town or city to proceed immediately to the scene of any local disaster for the purpose of screening the casualties to determine which are the more seriously injured and in need of immediate hospitalization, and which have minor injuries only and can be referred to the first-aid stations.

2. Emergency Hospital Units: Assign the members of the Active Professional Staff to Emergency Hospital Units in accordance with the blueprint for such an organization as outlined below.

a. The Surgeon and Assistant Surgeon.

The Orthopedic Surgeon.

The Internist and the Assistant Internist who are assigned to duty on their respective hospital services at the time of any disaster should comprise the group of professional men to be designated as the First Emergency Hospital Unit in each general hospital located within this state.

b. Auxiliary Emergency Hospital Units would be made up of the General Surgeon, the Assistant Surgeon, the Orthopedic Surgeon, the Ear, Nose and Throat Specialist, the Internist and the Assistant Internist who are on duty on their respective services at the other periods of the year, and each of these units should be assigned an on-call priority number which should change automatically, of course, each time when the major services at that particular hospital were changed.

c. Other specialists such as the Neuro-Surgeon, the Genito-urinary Surgeon, the Dental Surgeon, etc., whenever available on the active staff of a general hospital, should be kept on an on-call basis and summoned to the hospital only in the event one or more of any group of disaster victims had the type of injuries that might require any one of those specialized services.

b. Medical Director or Superintendent of each General Hospital to be requested to:

1. Summon immediately the members of the active staff assigned to the First Emergency Hospital Unit at that particular time and this unit should be expected to proceed immediately to its station within the hospital and to provide the necessary emergency medical care for the disaster victims as they were brought to the Hospital.

2. Summon the members of the Auxiliary Emergency Hospital Units in the order of their priority as additional surgical and medical help was required in the event it was obvious that the numbers of casualties were in excess of what could be handled by the members of the first emergency hospital unit.

3. Surgical-Medical Auxiliary Hospital Field Teams.

a. The members of the active professional staff of each general hospital within this state with bed capacity for 150 or more patients be requested to organize and be prepared to furnish on request of the State Director of Civil Defense and Public Safety or of his authorized deputy two or more Surgical-Medical Auxiliary Hospital Field Teams to be organized as follows:

1. Each Surgical-Medical Auxiliary Field Team should be composed of: One general surgeon, one assistant surgeon, one anesthetist and one internist.

2. Each Surgical-Medical Auxiliary Hospital Field Team should, as far as possible, be made up of clinicians who are not eligible for active military duty in the Armed Forces.

3. An Alternate Surgical-Medical Auxiliary Field Hospital Team would be required, for reasons which are obvious, for each general hospital which found it necessary to place members of their active professional staff on the roster of the surgical-medical auxiliary hospital team they organized.

b. The Surgical-Medical Auxiliary Field Hospital Teams when actually called to duty in the field would take over and operate an auxiliary hospital unit and would work with the State Civil Defense and Public Safety Director or his designated regional director.

4. Professional Clearing Station Field Teams.

a. The professional staffs of general hospitals within the state with beds for over 50 but less than 150 patients be requested to furnish two, while those with beds for less than 50 patients be requested to furnish one Professional Clearing Station Field Team to be organized as follows:

1. Each Professional Clearing Station Field Team should be composed of one surgeon, one assistant, and one other physician with a working knowledge of anesthesia.

2. Each such professional clearing station field team should be organized from those unqualified for military service as previously indicated.

b. Each professional clearing station field team would be expected to work in conjunction with their county Civil Defense and Public Safety Director and would take charge of clearing stations located in or closely adjacent to a major disaster area within their own or in immediately adjacent counties.

5. Professional First-Aid Field Team.

a. The county medical societies should be responsible for the organization of the necessary number of professional first-aid field teams required for their respective localities.

1. The professional first-aid teams would be made up of two general practitioners.

2. Each professional first-aid field team should be organized from those physicians and surgeons unqualified for military service as previously indicated.

b. These professional first-aid field teams would be expected to work in conjunction with the county Civil Defense and Public Safety Director in their immediate county or in a county immediately adjoined to that of their own in event of an emergency involving part or all of the state.

Dr. Daniel J. Sullivan then presented the supplementary report of the Committee on Emergency Medical Service, as follows:

This report is a supplement of the report made ready for publication in the Officers' and Committee Reports of the New Hampshire Medical Society for 1950. Since the report was submitted, a regional meeting of the American Medical Association Council on National Emergency Medical Service was held at the Hotel Statler in Boston on August 27, 1950. At that time, various members of the medical departments of the armed forces, members of the Atomic Energy Commission and members of the Red Cross were heard.

A great deal of discussion was given over to the problem of procurement of medical officers for the armed forces.

Since the meeting of the Committee on August 27, 1950, the so-called Guerney bill was, or in all probability will be, passed, and the Committee believes, with the majority of those people deliberating this question for some time, that the bill is fair and just in all respects, and finally sets up a yardstick to measure in an equitable way who shall and who shall not serve with the armed forces.

The Committee, therefore, believes that it is now up to Selective Service to get for the armed forces physicians in the numbers they believe that they require.

Another very important point made at this meeting was the tremendous number of skilled technical personnel that would be required in the event of an atomic-bomb disaster. It has been pointed out by the Committee in previous annual reports that the number of blood transfusions required after an atomic bombing would stagger the imagination. It therefore follows that the number of personnel skilled in the collection, processing, distribution and administration of the whole blood that would be needed would be tremendous.

In that connection, the Committee strongly emphasizes that training of these personnel must be undertaken without loss of time. To try to make specific recommendations and to form a policy that may be applied immediately the following recommendations are made: that all graduate nurses be given immediate instructions in the withdrawal of venous blood; that all graduate nurses be given instructions immediately in the intravenous administration of fluids and medications and in the administration of transfusions; that all nurses have the scope of their duties and responsibilities increased in every way possible; that all hospitals having training schools for nurses teach student nurses to withdraw venous blood and to administer intravenous fluids and medications; that nurses' aides now employed or now trained have delegated to them increasing responsibilities in the care of the sick, wounded and disabled in order to free graduate nurses for the increasing duties and obligations that they will undertake as soon as they are trained as above outlined; and, finally, that steps be taken to create and train large numbers of new clinical laboratory technicians.

The Committee urges the New Hampshire Medical Society to recommend and urge these new policies upon the hospitals within the State.

In support of the recommendations outlined above, it should be brought to the attention of the members that in a large-scale planning for disaster of the nature of an atomic-bomb attack on the civilian population, there will be great competition among many groups for the services of skilled and relatively skilled personnel. It must be realized that the services of these skilled people will be sought by those in charge of radiologic monitoring, civil air-raid defense, transportation, communications and other services vital to the preservation of the public health, morale and safety. It is therefore apparent that we must use our existing personnel for the functions that we in the practice of medicine must perform, and it is furthermore apparent that we cannot hope to gain a great many recruits from outside the profession and the ancillary professional services.

Therefore, it must be evident to all that the increase in the scope of the activities and the abilities of the personnel mentioned above must be sought for, since no other means of obtaining the personnel for getting these services performed will be available to us.

DANIEL J. SULLIVAN
CLARENCE E. DUNBAR
JOSEPH M. MCCARTHY
JOHN C. ECKELS
BERNARD J. MANNING

Dr. Brown stated that the Committee on Officers' Reports believed that there was a geographical concentration of membership of the Committee in the southern corner of the State, and suggested that there be a greater dispersion of the membership of the Committee in the State. At the present time, the members were from Nashua, Manchester, Concord, Laconia and Dover.

The Committee on Officers' Reports moved that the report of the Emergency Medical Service Committee, together with the supplementary report, be adopted, which meant that all the recommendations contained therein were to be carried out.

This motion was duly seconded.

Dr. Brown, in reply to a question, stated that the recommendations in the report were as follows: that the New Hampshire Medical Society seek active representation of the Civil Defense Advisory Council of the Governor; that the secretaries of the component county societies of the New Hampshire Medical Society be requested to invite Dr. Frank Corbin Moister to speak at their county society meetings on the subject, "Medical Aspects of Atomic Warfare"; and that, if the House of Delegates approved the organizational procedure outlined in Appendix A of the report, it give authority to this committee to seek the active support of the component county society committees on emergency medical service in the institution of this program.

Speaker Lewin then restated the motion to adopt the report and the supplementary report of the Committee on Emergency Medical Service.

The motion was duly seconded and was carried.

After considerable discussion President Bowler moved that the first recommendation of the Committee on Emergency Medical Service be referred to the Executive Committee of the Society for appropriate action.

This motion was duly seconded and was carried.

(To be concluded)

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society
Owned by the Massachusetts Medical Society and Published Weekly under the Jurisdiction of the Committee on Publications

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Subscription Terms: $8.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year.

Microfilm volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

Material, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

"DOCTOR DRAFT"

The communication from Dr. Thomas R. Goethals published elsewhere in this issue of the *Journal* is not so much in defense of the recently adopted amendment to the Selective Service Act of 1948 as it is a report on the necessity for it.

For some time prior to the passage of this amendment a shortage of medical officers in the armed forces had existed, and many admittedly eligible physicians had expressed themselves as waiting, instead of volunteering forthwith, for legislation that would outline this need and establish a method of meeting it. Some legal implementation was obviously necessary and has been accepted with almost total complacence, despite Dr. Coller's intimation that its passage constituted a slur on the medical profession.

The most amazing thing about the law is actually the very degree of complacency with which it has been accepted, for it represents discriminatory legislation the constitutionality of which might be questioned even if its necessity had become painfully apparent. For the pith of it is that citizens with a certain type and degree of education are now legally subject to draft as privates in the Army up to an age limit considerably higher than that which applies to the rest of the population.

Indication of this fact need not be taken as an indictment of discriminatory legislation. In the same category might come various forms of taxation such as the Harrison Act, which imposes on physicians a penalty for the privilege of relieving suffering.

Other laws or even generally accepted customs that discriminate in favor of a class, giving to it special privileges, are even less likely to be criticized by the group itself and are accepted by others if thereby the functioning in the common interest of that class of persons is intended to be improved. Such is the physician's customary exemption from jury duty.

The fact is that in times of emergency the knots that snarl the raveled skein of public necessity must often be cut in order to bring the thread into immediate use. The greater needs of the nation must be served despite the temporary suspension of some of the details of absolute equity that might otherwise make of democracy a thing of beauty and a joy forever.

In respect to the "doctor draft," even if the act of Congress that produced it suggests some indifference to military service on the part of the healing profession, perhaps that seeming indifference conceals a professional pride in being so essential to the defense of the country that special legislation is necessary to reveal its full importance!

FEDERAL REGULATION OF THE PRACTICE OF PHARMACY

The Massachusetts State Pharmaceutical Association has issued a statement to all retail druggists warning them that they may risk prosecution for violation of a federal law if they refill any prescription without specific authorization from the physician.

The Massachusetts law has always permitted a druggist to refill a prescription unless, in his professional judgment, it appeared unwarranted, or unless the physician had marked the prescription "N R" (not to be refilled). This practice can no longer be permitted according to the Food and Drug Commissioner. To the Pharmaceutical Association this ruling appears to be arbitrary, unreasonable and unnecessary. It disregards the professional responsibility of the pharmacist. It seems to represent an effort on the part of the federal Government to harass both pharmacists and physicians. The statement concludes:

> The way to kill a bad law or an unfair interpretation of the law is to enforce it to the limit. Public opinion, the patient, and the physician will all be in rebellion. . . [and in the meantime] we must advise all druggists to refrain from refilling all prescriptions unless the doctor indicates on the prescription that it may be refilled or unless the doctor, after being called on the telephone, consents to the refilling . . . Don't refill, under any circumstances, without calling the physician involved.

The Food and Drug Commission maintains that it is acting only for the protection of the public. Information has been accumulated regarding many cases of harm, even deaths, resulting from the indiscriminate and unauthorized refilling of prescriptions. The Council on Pharmacy and Chemistry of the American Medical Association has made the following statement:

> It is the duty and responsibility of the physician to determine whether or not the patient requires additional medication beyond that specified in the original prescription. The physician rather than the pharmacist should determine whether or not refilling of a prescription is indicated or warranted. A change in the condition of a patient frequently necessitates a change in dosage or medication; the repeated and indiscriminate refilling of prescriptions without the knowledge or the authorization of the physician is a practice which must be condemned.*

It is important for all physicians to understand these facts in order to avoid misunderstandings and the development of ill will. Physicians who receive calls from pharmacists (or patients) regarding renewal of prescriptions issued in the past should realize that there is no alternative under the present circumstances. Regarding prescriptions written in the future, they are reminded that the procedures outlined elsewhere in this issue of the *Journal* should be followed. So long as the present interpretation exists they should co-operate with the pharmacists to fulfill the law.

*Stormont, R. T., Secretary of the Council. Personal communication.

NOBEL PRIZE IN MEDICINE

THE prizes given annually in the name of Alfred Nobel have come to be considered the most highly valued honor that can be won by workers in the sciences, liberal arts and humanities in general. The 1950 award of the Nobel Prize in Medicine is of particular interest, not only because this year marks the fiftieth anniversary of the first Nobel awards but also because the work for which the prize is given is in a field that has for some time engrossed the attention of specialists in endocrinology and general practitioners alike. The recipients, Philip S. Hench, M.D., and Edward C. Kendall, Ph.D., of the Mayo Clinic, and Professor Tadeusz Reichstein, of Basel, Switzerland, are cited jointly "for their discoveries concerning the suprarenal cortex hormones, their structures and biological effects."

All three men have made outstanding contributions to the advancement of endocrinology. Dr. Hench, a pioneer in the use of Cortisone in the treatment of rheumatic diseases, was one of the first to apply ACTH to the therapy of these disorders. Dr. Kendall, the discoverer of thyroxin, and Professor Reichstein, working independently, discovered Cortisone.

American physicians and scientists of all countries join in the tribute to the winners of the 1950 award, given for tireless, patient investigation that has significantly advanced a vital field of medical science.

BLUE SHIELD ADDS ORAL SURGERY

IN an editorial in the November 2 issue of the *Journal* attention was directed to the new Plan B of Massachusetts Medical Service, whereby an additional group of service beneficiaries with family incomes of $3,000 to $5,000 was added to the general roster.

A still further benefit recently announced to subscribers is an oral-surgery rider effective between September 1, 1950, and August 31, 1951, providing for services rendered to a hospitalized bed patient by a registered oral or dental surgeon who has entered into agreement with Massachusetts Medical Service to furnish such services. At the direction of the Blue Shield and without further

notice the benefits contained in this rider may be extended beyond the date of expiration.

The voluntary insurance plans are in these ways steadily increasing their benefits, conservatively, safely, and in accordance with sound economic principles.

Italians do not trust each other out of sight, without written obligations. A milkman drives his cow to the door and milks in presence of the customer; and to prove the milk to be new, a calf is invariably tied to the cow's horns. Some of the calves, however, we Yankees believe, are more than a year old, and bear no relationship to their reputed mothers.

Boston M. & S. J., *November 27, 1850*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON PHARMACEUTICAL PROBLEMS

Refill of Prescriptions

The United States Government has taken steps to enforce a federal law interpreted by the Food and Drug Commissioner as requiring that a druggist must have a new prescription every time he dispenses drugs ordered by a doctor or complete directions in an original prescription authorizing refill.* Druggists who fail to live up to the letter of the law are threatened with prosecution. As a result, druggists are now telephoning doctors to obtain authorization to refill prescriptions.

When any doctor receives a call from a druggist he should either authorize the refill of the prescription or withhold authorization until he can check the patient's condition, and send or give the patient a new prescription if the medicine will be needed again in the future.

So long as the present interpretation of the law is in effect all prescriptions for medication to be used over a long period should carry a notation such as the following: "To be refilled as needed for ..... months" or "May be refilled ..... times."

Charles L. Brennan, M.D.
George L. Maison, M.D.
Frank N. Allan, M.D., *Chairman*

*If the prescription is not to be refilled the letters, "N R" should be written on it.
If "N R" is not written on the prescription the druggist is required by law to put "Warning — May be habit forming" on the bottle or box of medicine containing barbiturates and similar drugs.

BOSTON MEDICAL LIBRARY

NOBEL-PRIZE EXHIBITS

On December 10, the day of the award of the Nobel Prize in Medicine, the Library will place on exhibition the original writings of the winners of the 1950 prize, Philip S. Hench, M.D., and Edward C. Kendall, Ph.D., of the Mayo Clinic, and Professor Tadeusz Reichstein, of Basel, Switzerland.

Also exhibited will be the papers of Drs. George R. Minot and William P. Murphy on the liver diet in pernicious anemia, for which an earlier Nobel Prize in Medicine was given.

NEW HAMPSHIRE MEDICAL SOCIETY

DR. W. J. PAUL DYE

William Joseph Paul Dye, M.D., F.A.C.S., died on October 17, 1950. Dr. Dye was born in Sistersville, West Virginia, on November 10, 1902, the only son of Dr. Victor Hugo and Estelle (Riggin) Dye. He was educated in the public schools of Sistersville and received his bachelor's degree from the University of Wisconsin and his medical degree from Harvard Medical School.

Dr. W. J. Paul Dye

After an internship at the Massachusetts General Hospital and the Boston Children's Hospital, and residencies in two New York hospitals, he came to Wolfeboro in 1931, since when he has been the surgeon at the Huggins Hospital in Wolfeboro.

He was a fellow of the American College of Surgeons, certified by the American Board of Surgery, a member of the New England Surgical Society, Chairman of the New Hampshire Board of Registration in Medicine, secretary of the New Hampshire Surgical Club and of the Carroll County Medical Society, vice-president of the New Hampshire Medical Society and instructor in surgery at the Boston University School of Medicine.

He was a member of the Harvard Club of Boston and a past-president of both the Wolfeboro Rotary Club and the Kingswood Golf Club; he held membership in the Phoenix Lodge No. 73, A. F. & A. M., of Sistersville; Carroll Chapter No. 23, R. A. M., Wolfeboro; West Virginia Consistory; and Nemesis Temple Shrine. He was formerly a trustee of the First Congregational Church, and was a director of the Wolfeboro National Bank.

His widow, Ethel Clow Dye, his mother, Mrs. Estelle Dye, and two daughters, Mrs. William Garvey, of Durham, and Miss Mary C. Dye, of Wolfeboro, survive.

That Dr. Dye was held in high esteem by all of his associates is shown graphically by the positions of trust for which he had been chosen and by the throng that attended the memorial services in Wolfeboro. Physicians from all parts of the State and from Boston and New York came to pay their respects.

DEATH

WALKER — Wallis D. Walker, M.D., of Rye Beach, died on September 24. He was in his seventy-fifth year.

Dr. Walker received his degree from Harvard Medical School in 1901. He was a fellow of the American Medical Association.

His widow survives.

MISCELLANY

NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The following officers of the New England Obstetrical and Gynecological Society for 1951 were recently elected: president, Dr. Arthur T. Hertig, 21 Everett Avenue, Winchester, Massachusetts; vice-president, Dr. Joseph H. Howard, 144 Golden Hill Street, Bridgeport, Connecticut; treasurer, Dr. Frederick L. Good, 20 Commonwealth Avenue, Boston 16, Massachusetts; and secretary, Dr. Carmi R. Alden, 270 Commonwealth Avenue, Boston 16, Massachusetts.

CORRESPONDENCE

"AMERICANS FIRST"

To the Editor: "Doctors' Draft described as 'Slur' on Medical Men." This was the headline in the *Boston Globe* on October 24 introducing a news article quoting the retiring president of the American College of Surgeons. Dr. Coller had stated, in the *Globe's* words, that the "special bill to draft us was made law under circumstances that intimates indifference on our part."

It may be said at the outset that the American people as a whole have not been indifferent to the Communist invasion of South Korea. Regardless of antecedent circumstances involving our state of military preparedness, President Truman's decision to commit American troops to the support of the South Koreans was acclaimed by the nation as a whole.

The Selective Service Law of 1948 assured us of obtaining men for the ranks of the Army, Navy and Air Force. Congress acted without delay to pass appropriations to implement the expansion in strength called for by the Department of Defense.

There was, however, a dangerous shortage of doctors in service to give adequate medical support to forces in existence when the emergency arose, much less to the augmented force that were anticipated. The most urgent need was for doctors for the ground forces — that is, the Army.

Shortage of doctors for the Army was not, in early July, a new situation. Only a year before, the Department of Defense, aided by civilian medical societies, had made an effort to fill the shortage from young doctors who had been trained in the Army Specialized Training Program during World War II, at Government expense, and who had not seen fit to repay their obligation by serving in the armed forces. This effort had produced some recruits but not nearly enough to fill the vacancies then existing. That, however, was before the emergency occurred.

During July of this year the Army made a final attempt to obtain volunteers from this ASTP group, not only by direct approach by letter but also by enlisting the aid of certain senior officers of the reserve. It also canvassed junior medical officers of the reserve in an attempt to obtain volunteers. By the end of August, 1 former ASTP student had volunteered out of a pool estimated to number 3000. Twenty-nine reservists had accepted active duty. Five young doctors had been commissioned in the Regular Army. Seven physicians had applied for reserve commissions.

In August the Army was forced to recall to duty medical veterans of World War II, with or without their consent, pending action by Congress on several bills providing for registration and drafting of physicians. A lag of several months was foreseen, if the proposed legislation were passed, before drafted doctors could be made available. Medical support for the Army, however, could not wait.

On September 9 the President affixed his signature to the doctor-draft bill, making it law. On October 6 he announced that registration of all former ASTP's would take place on October 16. This has now been done.

So much for recent history. Was indifference shown on the part of the medical profession? The answer must be in the affirmative, at least so far as the ASTP group and the younger reservists are concerned. Had they volunteered in July as requested, the Army would have been able to fill all its existing medical vacancies, and would have had a generous reserve left over from which to fill vacancies in the inevitable augmentation of the military establishment.

Why did so few volunteer? There is no single answer to this question. Human nature being what it is, however, it is more than likely that the younger medical reservists, at least those who had seen service in World War II, thought it about time that men trained in the ASTP who had not served in the war or thereafter should precede them in offering their services. In any event, the reservists knew that they could be called at any time.

How about the ASTP's themselves? There was no legal provision, prior to passage of the doctor-draft law, requiring them to serve. One out of 3000 did volunteer, and deserves all credit for doing so. As to the others, a teacher of medicine has spoken for them. He stated, on the evening of October 24, at a Norfolk District Medical Society meeting, that this group did not care to volunteer unless they knew that all the rest would do so. This attitude, if it existed, sug-

gests that those who held it did not allow patriotic motives to override their individual interests.

What advice did the ASTP men who were interns, residents and research men in great civilian hospitals and medical centers receive from their chiefs when the question of volunteering was raised? Did these chiefs consider the needs of the armed forces first, or the interests of their own organizations, when they gave their advice? Is it possible that indifference to the country's needs was present even at the level of the medical schools and hospitals?

The answers to such questions as these, if obtainable, may give a clue to whether or not the doctor draft constituted a slur on medical men. As General Hershey has said, "Sooner or later, we must be Americans first and professional and scientific people second."

THOMAS R. GOETHALS, M.D.

Boston, Massachusetts

MAINE MARITIME ACADEMY CRUISE

To the Editor: I am writing again to request your assistance in obtaining a doctor to accompany us on our winter cruise. In the past two years your publication has been instrumental in obtaining the services of a doctor.

The cruise will be three months in duration and will make the following ports of call: Port au Prince; Colon, Canal Zone; Caracas, Venezuela; Ciudad Trujillo; Havana; Bermuda; Norfolk, Virginia; and Portland, Maine.

The training ship is provided by the United States Maritime Administration and is a very comfortable 400-foot steamer equipped as a training vessel with excellent medical equipment on board. Embarked will be the cadets, faculty and staff of the Academy, amounting to 220 persons. It has been the custom in the past to employ a doctor for this cruise, which is tantamount to a vacation for him owing to the fact that all persons on board are in excellent physical condition. However, we do desire a doctor on board in case of emergencies. The pay is $330 a month plus maintenance.

The cruise begins at Castine, Maine, on January 8, 1951, and ends at the same place on March 25.

W. W. WARLICK
Rear Admiral USN (Ret.)
Superintendent

BOOK REVIEWS

Psychoanalysis and the Social Sciences. Vol. 2. Managing editor, Geza Roheim, Ph.D. 8°, cloth, 329 pp. New York: International Universities Press, Incorporated, 1950. $7.50.

To anyone sincerely interested in obtaining a practical background of psychiatric principles, this book is invaluable. Bringing together the intimate connection between psychoanalytic concepts and anthropology, esthetics, history and sociology is as important as learning the basic principles of any scientific endeavor. No system of psychiatric study has any real meaning without an adequate understanding of its allied fields: the social sciences.

In this work the editor and his co-authors have made a searching and vital attempt to present a comprehensive picture of cultural differences together with their common denominators.

Contributions made by the social sciences to a better understanding of psychiatric problems have long been appreciated. Some of the most useful conclusions are here gathered together for consideration.

This is a reference volume that should be available at all times.

Introduction to Neuropathology. By Samuel P. Hicks, M.D., and Shields Warren, M.D. 8°, cloth, 494 pp., with 289 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1950. $10.00.

During World War II, one of the most active medical investigative and teaching centers was formed around the United States Naval and Georgetown University medical schools. A large collection of neuropathological material was available to the senior author, and this, in combination with the specimens from the Department of Pathology in the New England Deaconess Hospital, forms the basis for the book under consideration. Excellent photographic laboratories at both institutions provide the numerous and often superb illustrations. The text deals with fundamentals, as well as with secondary references to diseases and their clinical manifestations. The authors have been successful in depicting the reaction patterns in tissues of the nervous system, but are less fortunate in their attempts at integrating their often sketchy clinical concepts with the pathology of nervous disease. Illustrations do not always co-ordinate with the text, some are poorly chosen, and the best references to the literature are not always used. In general, the book gives evidence of faulty co-ordination and lack of clinical understanding. In Navy parlance, the book needs to be "buttoned up."

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Pathology: Application and interpretation. By Benjamin B. Wells, M.D., Ph.D., professor of medicine, University of Arkansas School of Medicine. 8°, cloth, 397 pp., with 32 illustrations. Philadelphia: W. B. Saunders Company, 1950. $6.00.

Studies from The Rockefeller Institute for Medical Research. Reprints. Vol. 139. 8°, cloth, 603 pp. New York: The Rockefeller Institute for Medical Research, 1949. $2.00.

Patterns of Panic. By Joost A. M. Meerloo, M.D. 8°, cloth, 120 pp. New York: International Universities Press, Incorporated, 1950. $2.00.

The Administration of Alcoholism Rehabilitation Programs. By Selden D. Bacon, Ph.D., associate professor of sociology, Yale University, and chairman, Connecticut Commission of Alcoholism. 8°, paper, 47 pp. New Haven: Hillhouse Press, 1949. $0.50.

Introduction to Psychosomatic Medicine. By C. Alberto Seguin, M.D., professor of psychosomatic medicine, University of San Marco, Lima. With a foreword by Flanders Dunbar, M.D. 8°, cloth, 320 pp. New York: International University Press, Incorporated, 1950. $5.00.

Visual Development. By J. H. Prince, F.R.M.S., F.Z.S., F.B.O.A., F.S.M.C. Volume I. With a foreword by Professor H. Hartridge, M.A., M.D., Sc.D., M.R.C.P., F.R.S., professor of physiology, University of London at St. Bartholomew's Medical College, and director, Vision Research Unit, Medical Research Council, etc. 8°, cloth, 418 pp., with 190 illustrations. Baltimore: Williams and Wilkins Company, 1949. $9.50.

A Primer of Venous Pressure. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, senior visiting physician, Charity Hospital, consultant in cardiovascular diseases, Ochsner Clinic, and visiting physician, Touro Infirmary, New Orleans. 8°, cloth, 174 pp., with 170 illustrations. Philadelphia: Lea and Febiger, 1950. $4.00.

Electrocardiography: Fundamentals and clinical application. By Louis Wolff, M.D., visiting physician, consultant in cardiology and chief of the electrocardiographic laboratory, Beth Israel Hospital, and associate in medicine, Harvard Medical School. 8°, cloth, 187 pp., with 110 illustrations. Philadelphia: W. B. Saunders Company, 1950. $4.50.

NOTICES

SCHOOL PHYSICIANS OF MIDDLESEX SOUTH

School physicians of Middlesex South will organize at a dinner meeting at 6:30, at the Smith House, on December 6. Mr. Edwin A. Nelson, Superintendent of Schools, Brockton, will be the speaker.

NEW ENGLAND CONFERENCE ON ALLERGY AND RELATED SUBJECTS

The third New England Conference on Allergy and Related Subjects will take place on Wednesday afternoon and evening, December 13. The afternoon program will consist of the presentation of cases illustrating the use of Cortisone and ACTH, with special emphasis on recent advances. This part of the program will be held from 3 to 5 o'clock in the Stearns Amphitheater of the New England Center Hospital, 171 Harrison Avenue, Boston.

The evening program will take place in the Sheraton Room of the Copley Plaza Hotel, Boston, at 8:30 o'clock. A symposium will be held on the practical and theoretical aspects of the use of ACTH and Cortisone in allergic conditions.

Arrangements have been made for a dinner at the Copley Plaza Hotel, Boston, for the convenience of those attending the program. Dinner will take place at 7:00 p.m., for which reservations may be made on or before December 11 by application to Dr. Irving W. Schiller, 65 East Newton Street Boston 18, Massachusetts, enclosing a check for $4.75 to cover the expense of the dinner.

All members of the medical profession are cordially invited to both the afternoon and the evening meetings.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, December 20, at 8:15 p.m. A symposium on the subject "Present Status of Antibiotic Therapy" will be presented. Dr. Maxwell Finland will act as chairman, and the speakers will be Drs. Harry Shwachman, Chester W. Howe and Alexander Rutenberg.

AMERICAN BOARD OF OPHTHALMOLOGY

Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a written qualifying test. These tests are held annually in January in various parts of the United States. Applications for the 1952 written test are now being accepted and must be filed before July 1, 1951.

Practical examinations will be held in San Francisco from March 11 to 16, in New York from May 31 to June 5 and in Chicago from October 8 to 13, 1951.

REGULAR CORPS EXAMINATION FOR MEDICAL OFFICERS IN UNITED STATES PUBLIC HEALTH SERVICE

A competitive examination for appointment of medical officers in the Regular Corps of the United States Public Health Service will be held on February 12, 13 and 14, 1951, at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates. Applications must be received no later than January 15, 1951.

Appointments will be made in the grades of assistant surgeon, equivalent to Navy rank of lieutenant (j.g.), and senior assistant surgeon, equivalent to lieutenant. In making assignments, consideration is given to the officer's preference, ability and experience; however, all commissioned officers are subject to change of station and assignment as necessitated by the needs of the Service. Appointments are permanent and provide opportunities to qualified physicians for a life career in clinical medicine, research and public health. Applicants who successfully complete this examination may ordinarily expect appointment as soon as they become eligible.

An applicant for appointment in the grade of assistant surgeon must be a United States citizen at least twenty-one years of age and a graduate of a recognized school of medicine with at least seven years of educational training and professional experience subsequent to high school. The requirements for appointment in the grade of senior assistant surgeon are the same except that at least ten years of educational training and professional experience subsequent to high school are required.

Applicants who will complete these requirements within nine months of the date of the written examination will be admitted, but may not be appointed until they meet the above requirements. Physicians who are successful in the examination and are now serving internships will not be placed on active duty in the Regular Corps until completion of internship. The examination will include an oral interview, physical examination and written objective tests covering basic medical sciences, including anatomy (except for appointment as senior assistant surgeon), physiology, biochemistry, microbiology and pathology, practice of medicine, including internal medicine (including neurology and psychiatry), therapeutics and toxicology, pediatrics and medical problems of obstetrics and gynecology, practice of surgery, including surgery, orthopedics, gynecology, obstetric procedures, and preventive medicine and public health.

Application forms and additional information may be obtained from the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. (Attention: Division of Commissioned Officers). Applications received after January 15, 1951, cannot be accepted.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 2–23. Springfield Hospital. Page 842, issue of November 23.

DECEMBER 4. Beth Israel Hospital House Officers' Colloquia. Page 798, issue of November 16.

DECEMBER 4. Hartford Medical Society. Page 680, issue of October 26.

DECEMBER 4. New England Cardiovascular Society. Page 841, issue of November 23.

DECEMBER 5. Tufts Medical Alumni Lecture. Page 841, issue of November 23.

DECEMBER 6. Massachusetts Physicians Art Association. Page 841, issue of November 23.

DECEMBER 6. School Physicians of Middlesex South. Notice above.

DECEMBER 7–9. New York State Society of Anesthesiologists. Page 582, issue of October 12.

DECEMBER 9. American Federation for Clinical Research. Page 680, issue of October 26.

DECEMBER 12. Harvard Medical Society. Page 841, issue of November 23.

DECEMBER 13. Rhode Island Medical Society. Page 842, issue of November 23.

DECEMBER 13. New England Conferences on Allergy and Related Subjects. Notice above.

DECEMBER 14. Treatment of Hyperthyroidism, Especially with Radioactive Iodine. Dr. Earle Chapman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

DECEMBER 18. Hartford Medical Society. Page 680, issue of October 26.

DECEMBER 20. Greater Boston Medical Society. Notice above.

JANUARY 3. Hampshire District Medical Society. Page 170, issue of July 27.

JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.

APRIL 9–13. American College of Physicians. Page 296, issue of June 15.

APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 24–26. American Goiter Association, Columbus, Ohio.

(*Notices concluded on page xi*)

NOTICES *(Concluded from page 898)*

OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 23.
FEBRUARY 27.
MARCH 27.
APRIL 24.
MAY 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 7

THURSDAY, DECEMBER 7

*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.

*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, DECEMBER 8

*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*12:00 m.–1:30 p.m. Surgical Pathological Conference. Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

*2:00–4:00 p.m. Therapeutic Conference. Joseph H. Pratt Diagnostic Hospital.

*4:00–6:00 p.m. X-Ray Conference. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, DECEMBER 9

*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

MONDAY, DECEMBER 11

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, DECEMBER 12

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, DECEMBER 13

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

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Index to Advertisers

	PAGE
American Policyholders' Insurance Co.	ix
A–Z Research Laboratory	viii
Baldpate, Inc.	x
The Blakiston Company	v
Boston Medical Supply Company	viii
Brown and Connolly, Inc.	ix
The Charles River Breeding Labs., Inc.	viii
Cutter Laboratories	iv
David Memorial Nursing Home	x
Glenside, Inc.	x
Hanover House, Inc.	x
Leary Laboratory	viii
Eli Lilly and Company	After viii
Mead Johnson and Company	Back Cover
The Medical Protective Company	v
National Discount and Audit Company	xi
The Nestlé Company, Inc.	ix
Perkins School	x
Ring Sanatorium	x
Sandoz Pharmaceuticals	ii
W. B. Saunders Company	Front Cover
Sharp and Dohme, Inc.	iii
E. R. Squibb and Sons	vi, vii
Walker–Gordon	v
Washingtonian Hospital	xi
Wiswall Sanatorium	x
Women's Educational and Industrial Union	viii
Woodside Cottages, Inc.	x

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